American Journal of Diseases of Children

Vol. 4 SEPTEMBER, 1912 No. 3

SOME FUNDAMENTAL PRINCIPLES IN STUDYING INFANT METABOLISM *

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Knowledge of the energy requirements of infants and the energy content of their food is of fundamental importance in studying their rate of growth and in the treatment of nutritional disorders.

The ideal method for determining the energy transformation of infants is that of direct measurement of the heat eliminated and produced. This involves expensive, elaborate apparatus, and has been possible in but one laboratory, that of Prof. Graham Lusk in New York. Undoubtedly, the cost of this extremely accurate and delicate apparatus will preclude its ever being used extensively in hospitals.

The other method that we wish to take up is that of so-called "indirect calorimetry," i. e., a computation of the energy transformations from the gaseous exchange. It is possible to compute with considerable accuracy the energy transformations of the infant from the amount of carbon dioxid produced, and particularly from the amount of oxygen consumed. Unfortunately, direct determinations of oxygen are difficult to carry out and require complicated apparatus. The direct measurement of oxygen in young infants has been but rarely determined. The principle work has been done by Professor Lusk[1] and an associate, Dr. John Howland,[2] in the respiration calorimeter at the Cornell University Medical School in New York, and recently in the respiration apparatus of Schlossmann and Murchauser[3] in Düsseldorf.

Direct determinations of carbon dioxid produced by infants are less difficult and have frequently been made in a number of foreign laboratories. Nearly all of our knowledge of infant metabolism is based on these investigations.

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*From the Nutrition Laboratory of the Carnegie Institution of Washington.

*Read at the meeting of the American Pediatric Society, Hot Springs, Va., May, 1912.

1. Howland: Proc. Soc. Exper. Biol. and Med., 1911, viii, 63.

2. Howland: Ztschr. f. physiol. Chem., 1911, lxxiv, 1.

3. Schlossmann and Murchauser: Biochem. Ztschr., 1908, xiv, 385; xviii, 1909, 489; 1910, xxvi, 14; 1911, xxxvii, 1 and 23; Schlossmann: Deutsch. Med. Wchnschr., 1911, p. 1633.

Practically all of the researches carried out on infants in which the carbon dioxid was measured, are open to serious objections, inasmuch as there was no proper control of the muscular activity.

In all previous determinations of infant metabolism, either of direct energy transformations or by means of the direct calorimetry, either no recognition has been given to the significance of muscular movements on

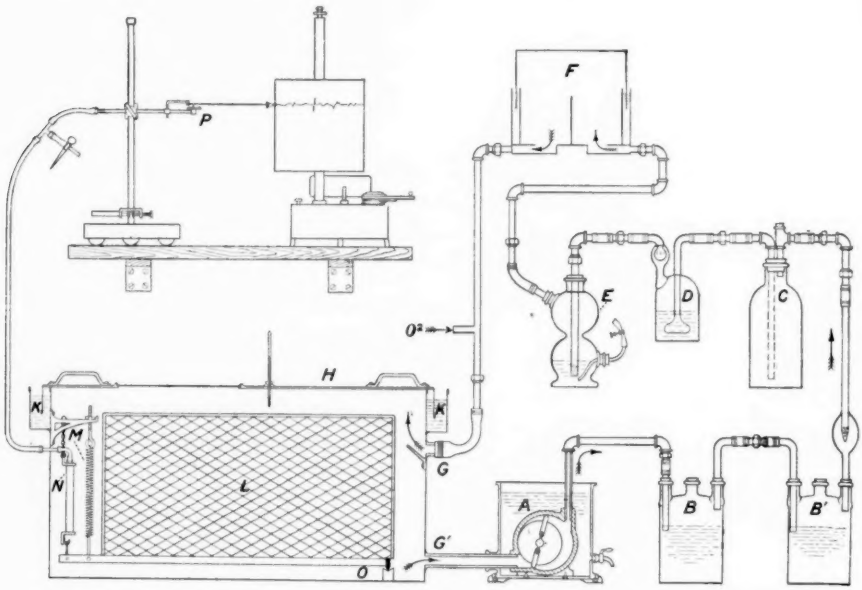

Fig. 1.—Diagram of respiration apparatus and absorbing system for determining the respiratory exchange of infants. The respiration chamber, L, in which the infant is placed is closed by a cover, H, which fits into a water seal, KK. One side of the cage, L, rests on a knife edge bearing, O, the other side being supported by a brass spring, M, fastened to a support. A tube pneumograph, N, is likewise attached to the cage, and any change in the center of gravity of the body of the infant produces an alteration in the tension of the spring, M, and the pneumograph, N. By air transmission, the tambour, P, moves a lever writing on the kymograph (the kymograph and tambour stand are drawn on a considerably enlarged scale). The air leaves the chamber at G′, enters the rotary blower, A, and then passes through sulphuric acid in two Woulff bottles B and B′. It then passes through the carbon dioxid absorber, C, and next into the drying vessel, D. Moisture is added in the vessel, E. The air then passes through a spirometer, F, which allows for contraction or expansion of air in the system and then to the respiration chamber through the opening, G. Oxygen as required is supplied through the opening O_2.

the part of the child, or it has been assumed that the child when not crying or obviously restless, was quiet and with constant muscular activity. In other words, the notes accompanying these reports said that the baby was either crying or quiet, i. e., asleep. The difficulties incidental to securing long experimental periods of constant muscular activity with

infants are only too well known, and yet an examination of the literature shows that almost invariably all of the longer experiments on infant metabolism have included periods of obviously great muscular restlessness and activity, as well as periods of crying. While it is not necessary to show that the metabolism of an active crying infant must of necessity be considerably higher than that of a quiet child, it is not so well known that it is wholly illogical to compare the metabolism of an active, restless, normal baby with that of a quiet, sick baby, since the amount of carbon dioxid excreted depends on the degree of muscular activity.

It is our purpose in this paper to point out the inconsistencies arising from the determination of carbon dioxid in infants without taking muscular activity into consideration. We are disposed, therefore, to question the desirability of long experimental periods for establishing the basal metabolism of infants when such periods may include not only quiet sleep, but also periods of activity and even crying. It is necessary at the outset to find what is the ideal length of the experimental period in the infant. This, we consider, is the period in which the baby is asleep, absolutely quiet muscularly, and free from even the slightest tremor, and preferably without food in the stomach. And, although it is difficult to secure these ideal periods over any length of time, fortunately it can be demonstrated that if this condition exists for twenty minutes or more, a reasonably accurate measurement of the metabolism may be secured with modern perfected apparatus. The apparatus in which the experiments were made (Fig. 1) was a slight modification of that described by Benedict and Homans for experiments on hypophysectomized dogs.[4]

It was used primarily to determine the amount of carbon dioxid excreted in the air and was furnished with means of recording graphically the amount of motion of the infant. The baby was placed in a cradle or crib, *L*, one end of which was suspended on a knife edge, *O*, and the other by a stout spiral spring, *M*. Parallel to the spiral spring was a tube pneumograph, *N*, which was connected with a delicate tambour, *P*, on the outside. Any changes in position of the center of gravity of the infant produced alterations in the tension on the spring, and the pneumograph, which transmitted this change to the tambour and pointer which made a graphic record on a smoked paper drum. This pointer can be made very sensitive to motion by simple adjustment of the spring and the leverage of the tambour and, indeed, Benedict and Homans were able to obtain the respiration rate of their dogs from the record. This apparatus records the infant's slightest muscular tremors, and we were able to demonstrate that a baby could have considerable slight muscular motion, which was sufficient to affect the metabolism, and yet be imperceptible to the eye.

4. Benedict and Homans: Jour. Med. Research, 1912, xxv, 409.

The babies in these researches were normal (breast-fed) babies obtained from the directory for wet nurses of the Massachusetts Babies' Hospital. The mothers of these babies were the usual type of wet nurse, all of whom had had a complete physical examination and a negative Wassermann reaction in the blood. The babies were all breast-fed with the exception of one or two who had one bottle of modified cow's milk in the twenty-four hours.

A great many determinations of carbon dioxid were made, and although the babies were awake in the morning, they did not sleep for any length of time in the afternoon, and only one or two successful periods were obtained in this manner. It was eventually necessary to work at night in a semi-darkened room where the infants kept quieter and slept for a longer time than during the day. They were all fed just before being put in the respiration chamber and consequently the results are somewhat vitiated by the specific dynamic action of the food in the stomach. In no instance were they kept in the respiration chamber when they showed any signs of discomfort, and the mothers watched the babies during the entire time that they were under observation.

It has frequently been noted in this laboratory, both with animals and with men, that there is a definite relationship between the pulse-rate and metabolism; we therefore commenced to record the pulse-rates of the infants. These were taken with a Bowles stethoscope placed over the heart of the baby, the tube of which was carried through the wall of the respiratory chamber and connected with ear pieces outside. The beat was counted for a period of one minute every three or four minutes during the entire period of the experiment. The relationship between the pulse-rate and the metabolism of the infant was found to be very close. The question then came up as to what was the minimum pulse-rate of a given age and how much and how long it could be affected by muscular exercise. We could find no literature on this subject, and a series of investigations was, therefore, instituted by one of us (F. B. T.), in which the pulses of a number of babies were counted by a skilled nurse at the Boston Lying-In Hospital and at the Directory for Wet Nurses at the Massachusetts Babies' Hospital. The wide fluctuations found in the pulse-rate of the baby, even during periods of sleep, were astonishing, and a series of curves pointing out these pulse-rates are given herewith (Figs. 2 and 3).

The two curves given herewith are samples of a larger series and illustrate the effect of muscular exercise on the pulse taken with a Bowles stethoscope from the heart of a very young baby and that of an older baby. The most striking fact in comparing these two curves is that there is much less stability of the young babies' pulse than that of the older ones, and a slight motion causes more marked elevation of the pulse. The minimum average pulse-rate depends on the age and type of the baby,

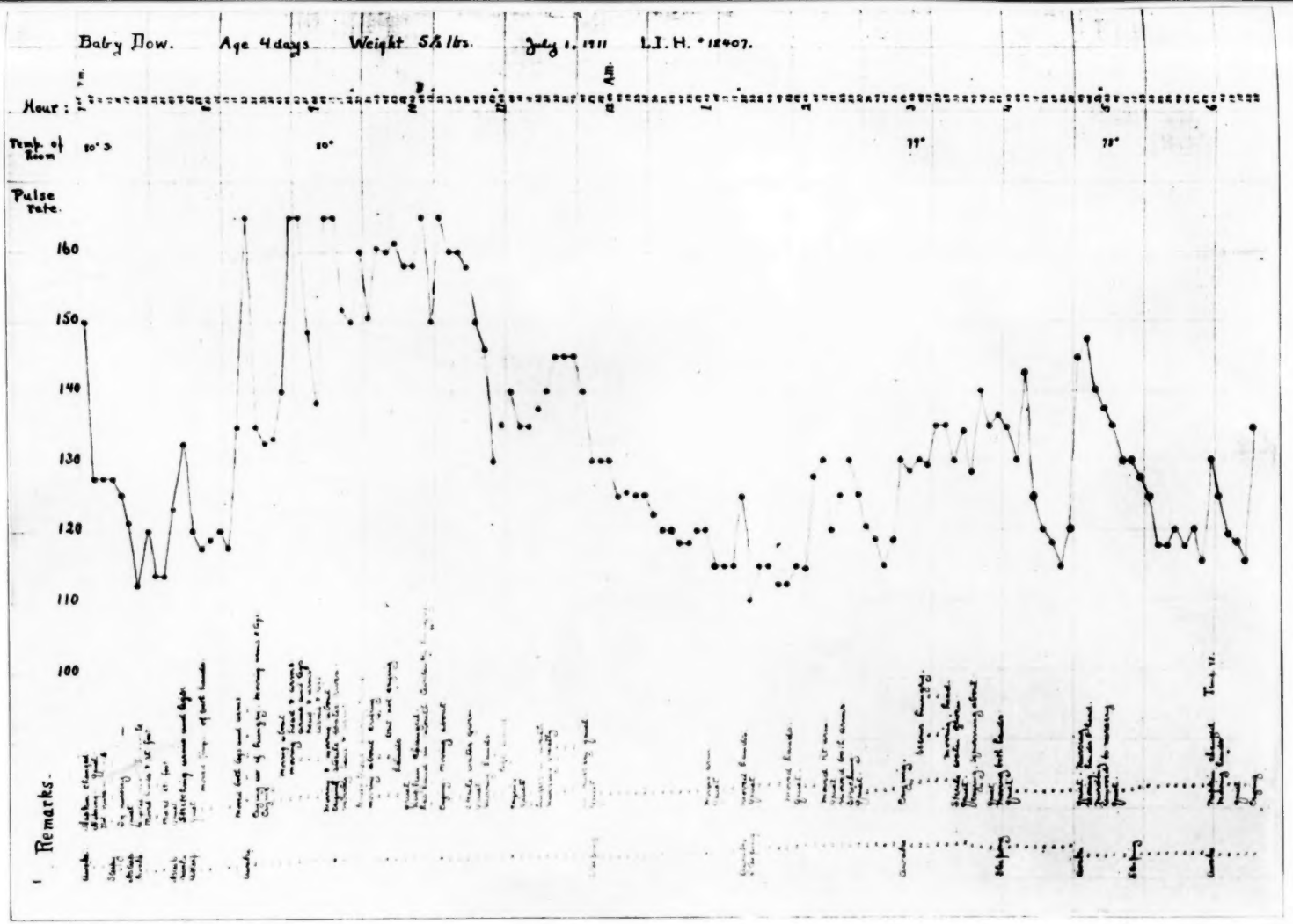

Fig. 2.—Pulse-chart of Infant Dow. Explained in the text.

and we believe that no general rules can be made, because each baby is a law unto itself. The average of the babies in the first week of life was 120 beats per minute and that of the older babies somewhat slower. The average minimum of one three-months-old baby was about 90 beats per minute, and that of another three-months baby 100 per minute. Slight movements which were visible practically always elevated the pulse-rate 10 to 20 beats, while violent exercise, such as nursing or crying, increased the pulse-rate 50 to 60 beats. When the pulse was increased for twenty minutes, as it was during a nursing, it took about ten minutes after the exercise was finished for the pulse-rate to reach the normal. Sometimes it dropped below normal after continued exercise, and remained there for three to five minutes. The pulse, therefore, did not reach the normal line in some instances until fifteen minutes after the muscular exercise was finished.

A very close relationship was found to be established between the carbon dioxid production, the pulse-rate and the muscular movements of the infant as recorded on the smoked paper drum. In so far as possible, only those periods in which the drum indicated minimum muscular activity were used for comparison. Under these conditions the relationship between the pulse-rate and the metabolism was very apparent.

A single record will demonstrate the interesting relationships above pointed out. Record 2 with Baby 5, November 16, 1911. The baby was placed in the chamber and after some time quieted down, and the first record commenced at the point marked *I* on the curve shown herewith (Fig. 4). The first period ended and the second began at point *II*. The results are given in the following table:

BABY 5. RECORD 2. NOVEMBER 16, 1911. WEIGHT NAKED 7.6 KILOS. AGE 7½ MONTHS

Period	Thirty Minute Periods	
	Pulse per Minute	Carbon Dioxid, Gms. per 30 Min.
1	117	3.49
2	108	2.73
3	113	2.97
4	122	3.24
5	117	3.33
6	130	3.41

Accompanying this are also given two kymograph records which show the graphic movements of the baby during the periods in which the carbon dioxid excretion was determined.

Period 1 represents the time between marks I and II on the chart. A close examination of the curve will show definite rhythmical movements which are unquestionably those of respiration. It is obvious that in Period 2, that is, from II to III, there was the minimum activity, and

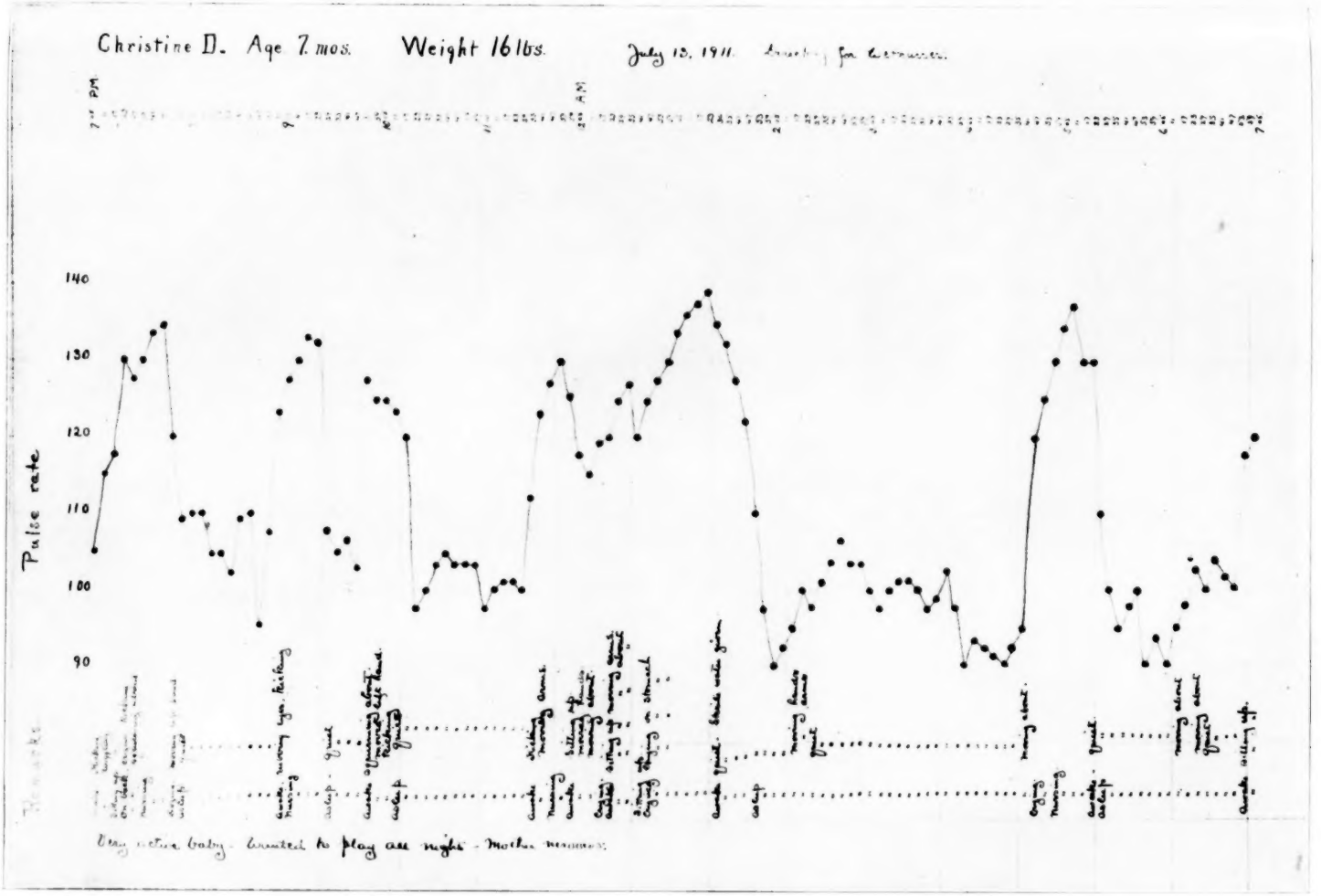

Fig. 3.—Pulse-chart in Infant Christine D. Explained in the text.

a comparison with the pulse-rate and carbon dioxid production shows that during this period there was the minimum pulse and the minimum carbon dioxid production. In fact, the agreement between the pulse-rate, carbon dioxid production and the graphic records on the curve is very striking. During the period from V to VI the graphic records showed a reasonably quiet period. On the other hand, during Period 5, which corresponds to this time, the carbon dioxid was slightly higher than during Period 4. This undoubtedly can be explained by the fact that the greatest activity during Period 4 was just before the end of the period, and unquestionably there was an accumulation of carbon dioxid in the chamber which was not swept out before Period 5 began. At this time residual analyses of the air in the chamber were not made, as it was found that the ventilation was sufficiently rapid to maintain the carbon dioxid content of the air at approximately .06 per cent. throughout the whole test. For extreme accuracy, it is obvious, therefore, that there should be a determination of the carbon dioxid at the end of each individual period. The excessive activity at the end of Period 6 was caused by the child's waking up and the last few minutes crying lustily.

While to the eye the child was "quiet" throughout all but the last period and apparently "absolutely quiet" in both Periods 2 and 3, the graphic records show considerably greater muscular activity during Period 3 than in Period 2, and enough to produce almost a 10 per cent. increase in the metabolism.

Although the results of our investigations on the whole are not yet ready for publication, we feel convinced of the importance of considering in all subsequent metabolism experiments the pulse-rate of the infant, and particularly the degree of muscular activity. The enormous variations in the total metabolism as affected by what might otherwise appear to be slight muscular activity, are such as to lead us to question seriously all experiments made in twenty-four periods, and we wish to assert that all metabolism experiments on infants made without known controlled pulse-rates and without graphic records of muscular activity are lessened enormously in value by the absence of these important factors.

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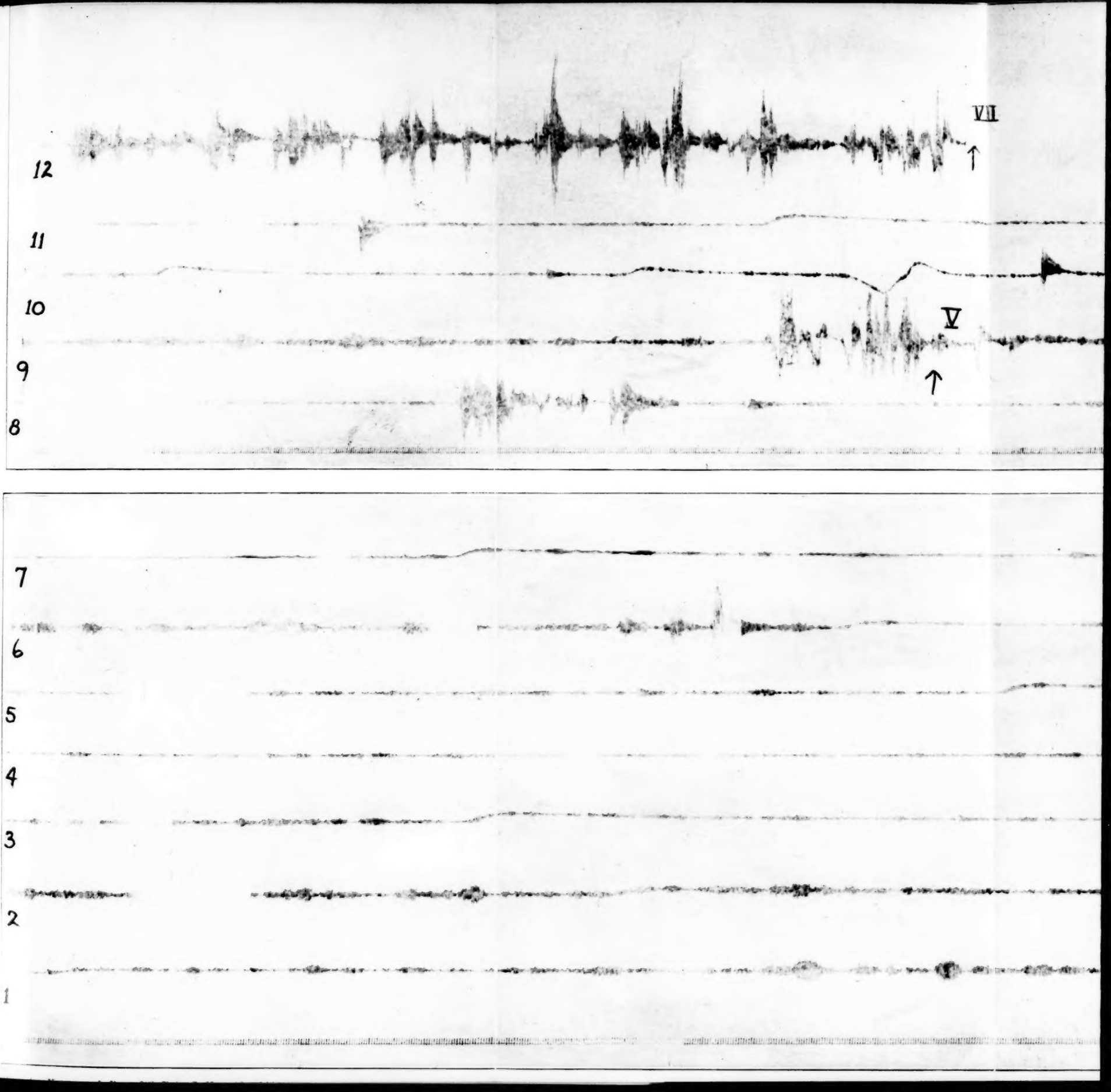
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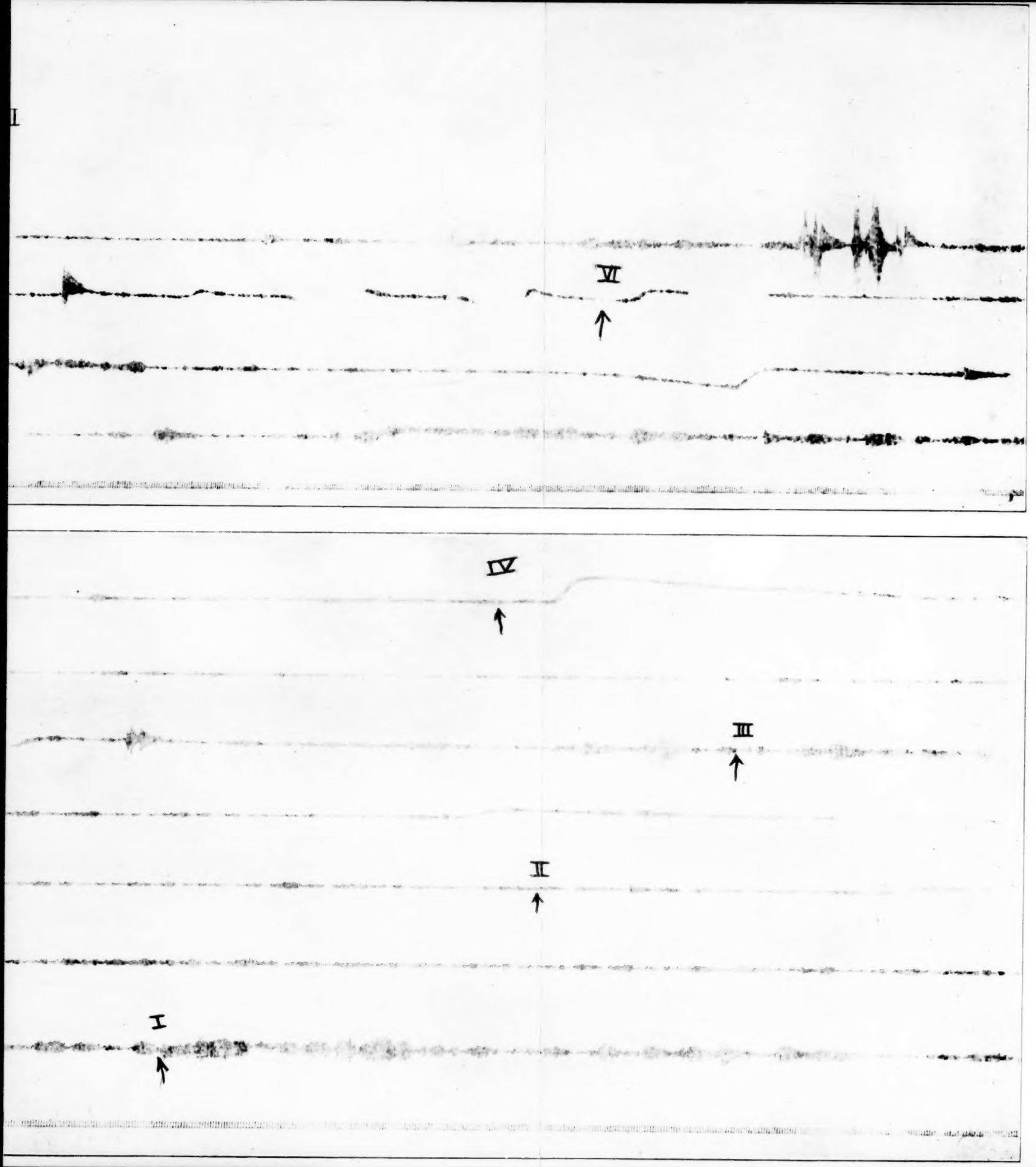
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CONGENITAL OBSTRUCTION OF THE POSTERIOR URETHRA: REPORT OF A CASE IN A BOY AGED FIVE YEARS *

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Urethral obstruction to the urinary flow may be brought about by a number of conditions. They are for the most part the result of inflammatory processes in the urethra itself, or of pressure on its lumen by the growth of surrounding structures, notably in prostate hypertrophy.

These changes acquired after birth are of frequent occurrence and are to be sharply distinguished from obstruction of the urethra present, although perhaps unrecognized, at the time of birth.

Without other reference to the interference with the urinary flow from gross malformation of the genito-urinary tract, and to the stricture of the urethra due to occlusion or narrowing of its external orifice, or of the pars navicularis, we wish to report an instance of a form of congenital membranous obstruction occurring in the prostatic portion of the urethra, because apparently this condition has not attracted the attention, at least in this country, that it deserves, and it may be that cases which might be relieved are not recognized.

CASE REPORT

History.—The case reported concerned a boy, F. S., aged 5 years. His family history was good; his father and mother were living, five brothers and four sisters were alive and well, and had no symptoms similar to those of the patient. The birth was normal. From infancy it was noted that there was frequency of micturition. It was necessary for the patient always to wear napkins, which were wet, according to the mother's statement, "about every half hour." The urine was described as often being "thick and milk-like." Otherwise the patient's life was uneventful until 3 years of age, when he had measles. Following this illness the patient seemed susceptible to colds and had much of the time a purulent discharge from the left ear.

He first came under the observation of one of us on June 26, 1911, when at the age of 4 years, he was admitted to The Thomas Wilson Sanitarium complaining of loss of weight and strength and moderate diarrhea.

Examination.—On examination the boy was found to be sparely nourished, pale and with evidences of rickets—marked Harrison's grooves and a moderate rosary. His weight was 23 pounds. The lungs and heart were normal. The abdomen was considerably distended and pendant.

On palpation in the left lumbar region there was made out a soft movable lobulated mass extending from the anterior superior spine to the costal margin and to about midway between the umbilicus and the lateral border of the abdomen. This mass could readily be brought between the fingers in bimanual palpation; its borders were rounded and it was a little sensitive on pressure and dull on per-

* From The Thomas Wilson Sanitarium and the Medical and Pathological Departments of Johns Hopkins Hospital.

cussion. On the right flank a similar smaller mass could be made out emerging from the lower border of the liver.

A third rounded mass was detected in the mid-line extending from the symphysis pubis to the level of the umbilicus. This was oval in shape and regular in outline, freely movable and suggested an enlarged urinary bladder.

The liver was readily palpable 3 cm. below the costal margin and was not tender. The spleen was not enlarged.

External genitalia were normal. The patient had no fever and there was no history of intestinal obstruction.

Urine examination was important. The urine was slightly turbid and of low sp. gr. (1,002 to 1,004) and acid in reaction. It contained but a trace of albumin and no sugar. On microscopical examination a large number of pus cells were found, a few epithelial cells and red blood corpuscles. There were no casts. The amount of urine collected for twelve hours was 350 c.c. No tubercle bacilli were found in a centrifuged specimen. An attempt was made to catheterize the patient but the external meatus was too small to admit the smallest catheter available. There seemed to be at that time little interference with the flow of urine; no vesicle tenesmus was noted and there was no undue sensitiveness over the bladder.

A von Pirquet skin test was negative.

The urinary findings suggested a cystitis or pyelitis. The presence of the lobulated tumors above described in the flanks made the diagnosis of congenital cystic kidneys a possibility.

No marked change was noted in the patient's condition for several days, after which the lateral masses became smaller and finally could hardly be detected. Their reduction in size was apparently associated with the more thorough emptying of the bowels, although during the time of observation of more than two weeks there had been a formed or semi-formed large stool every twenty-four hours. Slight variation in the size was noted from day to day also in the fluctuating mass above the symphysis pubis.

The child's general condition bettered. His appetite was good and he was discharged improved on July 13. The clinical diagnosis at the sanitarium was: Pyelitis, hypertrophy and dilatation of bladder, rickets, intestinal indigestion with distention and partial fecal impaction.

The patient was not seen again until January, 1912, an interval of more than five months.

At this time he came to the children's out-patient department, The Johns Hopkins Hospital. He looked pale and extremely ill. The history was that although he had not been strong he had had no acute illness until two weeks before, when there had developed a cough and abdominal pain. He had since that time become progressively worse.

He was admitted to the service of Dr. Barker January 3. On examination the boy was much emaciated. The breath-sounds were harsh and accompanied by a few moist râles. The abdomen was distended and a number of soft masses thought to be intestinal coils were made out on palpation.

Above the symphysis and extending nearly to the umbilicus was the same oval mass before noted, apparently a distended bladder. The blood examination was as follows:

Red blood corpuscles	5,100,000
Leukocytes	11,000
Hemoglobin	70 per cent.

The urine contained a large number of pus cells and a trace of albumin.

There was a purulent discharge from each ear, a large abscess in the left tonsil and a mucopurulent exudate on both tonsils and the pharynx.

The Wassermann reaction was negative. The patient was given bismuth by mouth and the motility of the intestines determined by *x*-ray examinations.

The stomach appeared slightly distended. The motility of the small intestines seemed normal. The sigmoid flexure of the colon was displaced somewhat to the right and there seemed to be an unusual stasis between the sigmoid and the rectum.

This condition helped to account for the large lobulated mass in the left flank which gradually disappeared when the bowel was thoroughly evacuated. There was some phimosis and the patient was circumcised.

The child did not improve in the hospital. On several occasions acute dilatation of the stomach was noted and shortly before exitus on January 18, there were repeated convulsive spasms.

The temperature did not rise above 99 F., nor did the pulse exceed 120 to the minute.

PATHOLOGICAL FINDINGS

Necropsy (3670) was performed ten hours after death by Dr. Sprunt.

Anatomic Diagnosis.—Congenital malformation with obstruction of the prostatic urethra; dilatation and hypertrophy of the bladder and ureters; bilateral hydronephrosis; chronic posterior urethritis, cystitis, ureteritis and pyelitis; bilateral chronic suppurative otitis media; cloudy swelling of viscera; emaciation; unilateral congenital cystic kidney; chronic pleural adhesions; operative scar of circumcision; acute anterior urethritis; adenoma of right adrenal.

The body is that of an emaciated male child, 80 cm. in length. There is no subcutaneous edema. The prepuce has been recently removed; otherwise the external genitalia seem normal on inspection and palpation.

After opening the abdominal cavity the viscera are found normally disposed, excepting the cecum, which lies in the left lower abdominal quadrant, is quite freely movable and can easily be brought back to its usual position. The bladder is very large and extends half way to the umbilicus. By firm pressure on the bladder a very small stream of urine can be expressed from the external meatus of the urethra. On following the sigmoid flexure into the pelvis it is thought at first that it turns on itself and runs back upward toward the right kidney, but after further dissection, this structure is found to be an enormously dilated and hypertrophied ureter of about the same size as the sigmoid flexure of the colon.

Examination of the brain and meninges reveals no abnormalities. Except for pleural adhesions on the right side and a mild grade of bronchitis, the thoracic viscera are normal. The heart weighs 70 gm.

The spleen, pancreas, stomach and liver show nothing noteworthy. The adrenals are normally placed. The medulla of the left adrenal is softened. About the center of the right adrenal there is an irregular thickening, roughly 1.5 cm. in diameter, which seems fused with the kidney capsule beneath it. It resembles in general the adrenal cortex but with less regular markings and with rather coarse, white strands running through it.

The organs of the urinary system were carefully dissected and a sketch made of them *in situ* by Mr. J. T. Webster of the Johns Hopkins Medical School (Fig. 1). The kidneys are in their normal position and are both enlarged, but are not exactly alike. The larger size of the left kidney 9x4.25x3.5 cm., is only partly explained by the formalin injection of its ureter under slight pressure. On palpation the kidneys give a distinctly fluctuating sensation as if the organs were merely thick-walled sacs. The fetal lobulation is easily seen on both and on the surface of the smaller right kidney, 7x5x2.5 cm., there are several thin-walled cysts, the largest measuring 2 cm. in diameter. On longitudinal incision both kidneys consist of a mass of dilated cystic spaces, evidently the dilated calyces which are continous with the ureter below. The whole thickness of the kidney parenchyma, from calyx to capsule, averages from 5 to 7 mm. with occasional thicker areas, measuring 15 mm. between the larger calyces. The structure of cortex and medulla cannot be distinguished. The blood-supply of the kidneys seems quite normal.

The ureters show the normal relationship to kidneys and vessels; they are very tortuous in their course but otherwise follow the normal path. They are greatly enlarged, of the same size, 1.5 cm. in diameter, and have firm, thick walls.

The bladder was opened longitudinally along its anterior wall while *in situ*. It measures 7 cm. in length from internal meatus to apex. There are scattered ecchymoses in the mucosa which is elsewhere quite pale. Beneath the mucosa the musculature is thrown up into very prominent trabeculæ. The ureteral and urethral orifices are in their usual relative positions. A small probe is easily passed into the ureters from the bladder, but in the urethra meets with an obstruction in the lower prostatic portion. Similarly when the urethra is sounded through the external meatus, an obstruction is encountered in the same region. The whole urinary tract is then removed *en masse*, including half of the anterior urethra and opened along the anterior wall.

Through the wide internal meatus the bladder becomes continuous with the greatly dilated and thick walled prostatic urethra which forms an oval sac with the distal, blind extremity 2.5 cm. from the internal meatus. The floor of this pouch shows several prominent folds near the midline which end below in an unusually prominent verumontanum which reaches three-fifths of the distance from the internal meatus to the blind end of the sac. The opening of the vagina masculina is conspicuous, shaped like a crescent, with the concavity directed upward. Numerous orifices of the prostatic ducts are observed on each side of the verumontanum but those of the ejaculatory ducts are not seen. Immediately below the verumontanum, the ridge, of which it forms a part, divides into two prominent diverging folds which soon fuse with the anterior wall of the urethra instead of fading out gradually on the posterior wall of the membranous urethra as usual. Just below the verumontanum between the diverging folds, there is a small equilateral triangular opening whose sides measure about 3 mm. A probe passed through from the anterior urethra presents in this opening and abuts against the hypertrophied verumontanum. This is the only communication between the anterior and posterior portions of the urethra.

The mucosa of the dilated prostatic urethra is pale and resembles that of the bladder in appearance. The mucosa of all that portion of the urethra anterior to the obstruction is swollen, reddened and shows small ecchymoses.

The anus and rectum seem quite normal. Nothing unusual is noted about the seminal vesicles or vasa deferentia.

MICROSCOPIC DESCRIPTION

Urethra: Sections were prepared from the lower end of the prostatic sac; through the folds immediately below the verumontanum; through the distal portion of the verumontanum; and through the proximal end of the same structure. The blind end of the prostatic urethra is clothed with stratified pavement epithelium similar to that of the esophagus. The folds below the verumontanum are covered with the same type of epithelium but that of the anterior urethra is so badly desquamated that its nature cannot be definitely determined. Over the verumontanum and the rest of the prostatic urethra, the usual type of epithelium is present. The subepithelial tissues everywhere consist of a very dense, fibrous tissue with few elastic elements. Small clusters of mononuclear cells may be found occasionally beneath the epithelium. The vagina masculina is not prominent. Indeed, it is less conspicuous than is often the case.

Bladder: The bladder wall is thick, the muscle bundles large. The mucosa shows scattered mononuclear cells. The epithelium of the mucosa is not preserved.

Ureter: The ureter, also, is greatly thickened and contains many elastic fibers. The epithelium is of the normal type and very well preserved.

Kidney (Fig. 2): Examination under a dissecting lens reveals the whole width of kidney parenchyma much narrowed. The medullary portion is no longer pyramidal in shape but is flattened out, the tubules running almost parallel with the

lining of the dilated calyces. The tubules of the cortex are enormously enlarged being quite prominent even under the power of the dissecting microscope. With higher power the epithelium of the pelvis is found well preserved. Beneath it the mucosa is infiltrated with plasma cells and contains no elastic elements. The connective tissue between the straight tubules in the medulla is thickened and contains scattered mononuclear cells. The walls of the larger blood-vessels are thickened. This is especially true of the intima. The capsule of the kidney is considerably thickened and extending down from it in places may be seen strands of connective tissue. Between these connective tissue strands the tubules are markedly hypertrophied with wide lumina and very large cubical or flattened granular cells, whose nuclei stain well. The lumen of each tubule contains a foamy material and occasionally a hyaline cast. The glomeruli are few in number, but those present seem very nearly normal. Here and there one which is imbedded in a connective tissue strand is entirely hyaline or shows some hyaline change.

Sections from other organs show nothing of interest in this connection, save, perhaps, those from the right adrenal. The tumor-like nodules consist of large nests of epithelial cells separated by connective tissue trabeculæ, some of which are extensively calcified. The appearance and arrangement of the cells is strongly suggestive of the normal adrenal cortex. The cells, however, contain practically no fat or lipoid substances.

SUMMARY OF CASE

In summary, we present the case of a boy 5 years old, who had had difficulty in controlling micturition from infancy. Urine passed every half hour of day and night, and was attended by no pain.

Four weeks before death there occurred a sudden onset of the terminal illness with cough, abdominal pain, vomiting and constipation. Physical examination showed malnutrition, purulent conjunctivitis, discharge from left ear, tonsillar abscess, protuberant abdomen, a tumor above the symphysis, with dull percussion note, redundant foreskin with phimosis; hemoglobin 70 per cent. There was no fever. Later vomiting became frequent, there were many convulsive attacks and breathing suggestive of air hunger. He was circumcised three weeks before death with the result of slightly improving the flow of urine. Attempt at catheterization failed.

At autopsy there was found an obstruction in the prostatic portion of the urethra, which was converted into a blind pouch by the fusion of its anterior and posterior walls, due apparently to an overdevelopment of folds normally present immediately distal to the verumontanum. A small triangular opening whose sides measured 3 mm. situated in the floor of this pouch was the only communication with the anterior urethra and through this the urine must pass. As a result of the urinary stasis there had occurred marked dilatation and hypertrophy of bladder, ureters and kidney pelves with typical hydronephrosis terminating in uremia.

Aside from the condition in the urethra, no other congenital anomaly was discovered unless the adrenal adenoma may be so considered.

INCIDENCE OF CONGENITAL URETHRAL OBSTRUCTION

While the condition here described and other types of congenital urethral obstruction cannot be considered of frequent occurrence, neither

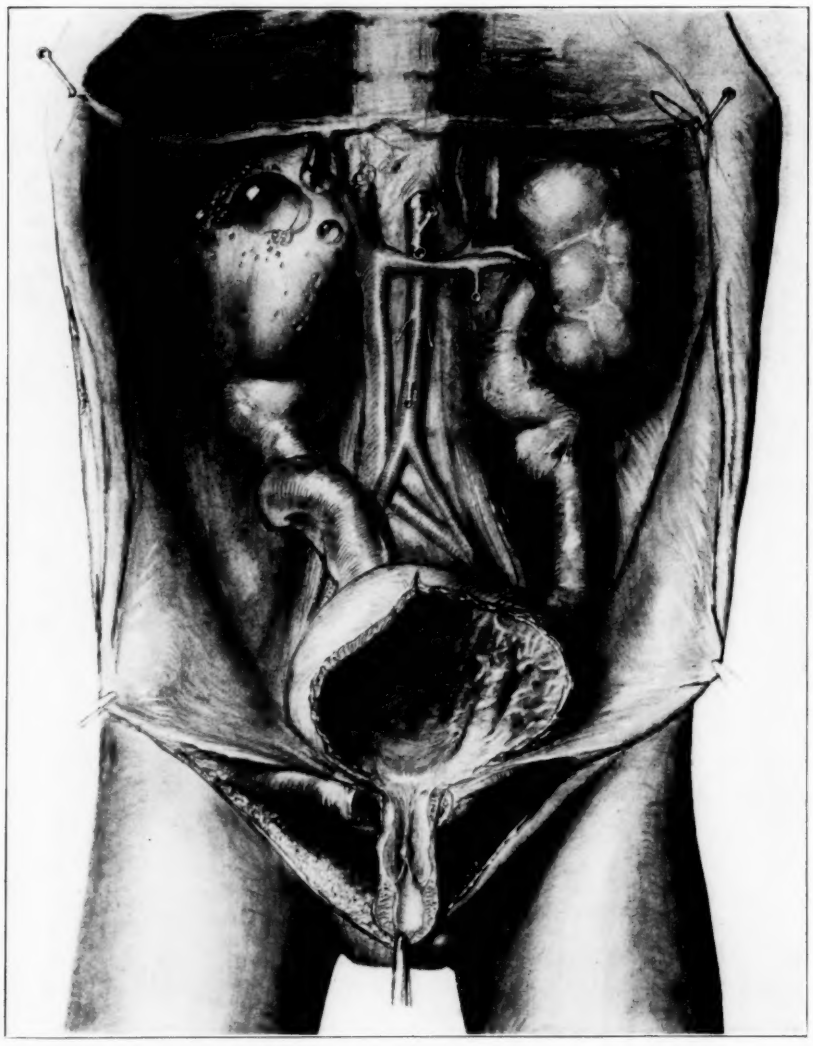

Fig. 1.—Drawing at autopsy by T. J. Webster. Note the enlarged, lobulated cystic kidneys, the enormously dilated and tortuous ureters; the hyertrophied, distended bladder and the hypertrophied membranous folds in the prostatic urethra constituting the obstruction to the urinary flow.

are they excessively rare and we feel, after reviewing the literature, that they may be met with more frequently than is generally supposed.

Very similar cases, some of them almost identical with ours, are reported by Wilckens,[1] Lederer,[2] Tolmatschew,[3] Bednar,[4] Godart,[5] Budd,[6] Velpeau,[7] Schlagenhaufer,[8] Commandeur,[9] Bonnet,[10] Reboul,[11] Fuchs,[12] Porak,[13] Lindeman,[14] Picard.[15] In addition Bazy[16] reports six cases, in older boys and in men, which he had observed clinically, as cases of congenital stricture in the region of the pars membranacea or pars bulbosa and emphasizes the importance of congenital strictures of the urethra even in adults. Ebert[17] reports a similar clinical case in which he punctured the obstructing membrane and discharged his patient as cured. There are numerous other reports of congenital stricture in the anterior urethra, due to valvelike structures, partial or total occlusion of the urethra throughout a smaller or greater portion of its extent, atresia of the external meatus, etc. Englisch,[18] in a recent exhaustive article, has collected a large number of cases of congenital narrowing of the male urethra.

Most of the published observations similar to the case here recorded occurred in new-born children, or babies a few days or weeks old. A number, however, have been observed in older children, in whom the lesions seem to have remained latent for a time and then gradually became

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1. Wilckens: Zur Frage der kongenitalen Stenosen der männlichen Harnröhre. Ztschr. f. Urol., 1910, iv, 814.

2. Lederer: Ueber eine angeborene membranöse Verengerung der Pars prostatica urethræ. Arch. f. path. Anat. u. Physiol., Berl., 1911, cciii, 240.

3. Tolmatschew: Ein Fall von semilunaren Klappen der männlichen Harnröhre und von vergrösserter Vesicula prostatica. Arch. f. path. Anat. u. Physiol. Berl., 1870, xlix, 348.

4. Bednar: Quoted from Wilckens,[1] Lindeman,[14] et al.

5. Godart: Valvule anormale dans le canal l'urètre. Bull. Soc. anat. de Paris, 1854, xxix, 137.

6. Budd: Quoted from Wilckens,[1] Lindeman[14] et al.

7. Velpeau: Traité d'anatomie chirurgicale, Paris, 1826, ii, 297.

8. Schlagenhaufer: Ein Beitrag zu den angeborenen Klappenbildungen im Bereiche der Pars prostatica urethræ. Wien. klin. Wchnschr., 1896, No. 15, p. 268.

9. Commandeur: Dilatation de l'appareil urinaire chez le foetus par rétrécissement valvulaire congénital de l'urètre. Lyon méd., 1898 Mars. 13.

10. Bonnet: Quoted from Wilckens.[1]

11. Reboul: Quoted from Wilckens.[1]

12. Fuchs: Zwei Fälle von kongenitaler Hydronephrose. Inaug. Dis., Zurich, 1900.

13. Porak: Quoted from Commandeur and Lederer.[9]

14. Lindeman: Casuistischer Beitrag zur Frage der angeborenen klappenförmigen Verengerung der Pars prostatica urethræ. Inaug. Dis., Jena, 1904.

15. Picard: Convulsions à forme eclamptique chez un homme, Gaz. méd. de Strassburg, 1855, No. 7, p. 259. Quoted from Lindeman.[14]

16. Bazy: Rétrécissement congénital de l'urètre chez l'homme. Presse méd., 1903, p. 215.

17. Ebert: Quoted from Segall. Ein Fall von angeborener Harnröhrenverengerung. Inaug. Dis., Königsberg, 1890.

18. Englisch: Ueber angeborene Verengerungen der männlichen Harnröhre. Folia urologica, 1909, iv and v.

more severe. Budd's patient was 16 years old, Lederer's 11, Wilckens' 2¼, our one case 5. Picard regarded the valve-like lesion in his 40-years-old patient as of congenital origin. The symptoms are dated in three of these cases from an attack of one of the acute infections.

SYMPTOMATOLOGY

Of the instances observed in older children, the case here reported is quite typical if we accept those symptoms due to the local infections in the middle ear, tonsils, etc. In the new-born infants and babies a few

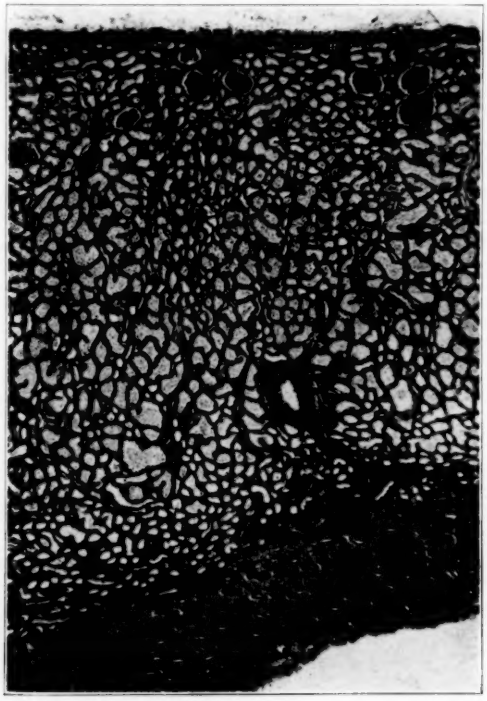

Fig. 2.—Section of kidney under low power. The glomeruli appear normal; tubules of cortex are greatly dilated; tubules of medullary portion are compressed and run parallel to lining of dilated calyces.

days old the symptoms are of course simpler and consist in the extreme cases of failure to pass any urine whatever.

PATHOLOGY

Englisch[19] divides all congenital obstructions in the urinary passages of children into two great groups:

A. Obstructions which exist in embryonic life, but later disappear.

B. Obstructions which remain permanently.

19. Englisch: Quoted from Wilckens.[1]

Under Group "A" he includes the fusion of epithelial folds in the ureters; a similarly produced atresia of the ureteral opening into the bladder; valve formation and kinkings of the ureters which disappear with subsequent growth; atresia of the internal or of the external meatus of the urethra; atresia of the prepuce; and finally atresia of the orifices of the utriculus masculinus and of Cowper's glands.

Under Group "B" are found the valves and stenoses. The valves occur at the transition between ureters and kidney pelvis, rarely in the bladder; especially in the prostatic part of the urethra at the upper and lower ends of the colliculus seminalis; in the anterior urethra at the end of the fossa navicularis, at the external meatus and even in the foreskin.

The places of predilection of the stenoses in the urethra are especially the point of union of the pars membranacea with the pars bulbosa, the posterior end of the fossa navicularis and the external urethral orifice.

The folds or valvelike obstructions in which we have been most interested seem to occur in those regions where folds or ridges are normally found in the urethral mucosa; and this is especially true of the anterior end of the colliculus seminalis where most of these obstructions are encountered. Here in the normal urethra there is a division of the crista urethralis into two ridges which, becoming less and less prominent, gradually fade out in the posterior wall of the bulbous urethra.

In most of the reported cases of obstruction at this point, the lesion seems to have been produced by an overdevelopment of these folds which fuse with the anterior wall with the formation of membranes extending across the urethral lumen. The resulting structures vary slightly in individual cases. Schlagenhaufer describes the obstruction in his case as due to a funnel-shaped valvular occlusion. In others the pressure of the urine has resulted in a more definite pouch, with this concavity of the membranes directed backward toward the bladder. The size and relationships of the opening through the obstruction vary also, and this is of considerable practical importance in the clinical examination. A sound introduced into the urethra may pass quite unhindered into the bladder, as in the case reported by Bednar, or the opening may be so small and so situated immediately below an enlarged verumontanum, as in our own case, that the smallest catheter is obstructed.

Budd, Godart and others compare the obstructing membrane to the valves of a vein or to the semilunar valves of the heart. In these cases no interference is offered to the passage of an instrument from below.

The secondary pathologic changes are quite uniform in kind, differing only to a certain extent in degree. There is invariably dilatation and hypertrophy of the higher urinary passages with bilateral hydronephrosis.

Histologic examination shows a metaplasia of the epithelium in the posterior urethra from the usual transitional type to a stratified squamous type like that of the epidermis.

GENESIS

The occurrence in young children and the similarity of the pathologic anatomic pictures in different cases establish the lesion as congenital and suggest strongly that it has its origin in some slight variation from the normal in the course of development. It must then be through study of the embryology of this region that we shall finally arrive at a satisfactory explanation for these anomalies. At present this is not to be found.

Certain forms of obstruction in the prostatic urethra have a ready explanation in the present state of our knowledge of embryology. Those due to the abnormal persistence of Müller's ducts in the male come under this class. In an over-development of the sacculus prostaticus, the homologue of the vagina, this structure may become so large that it is pushed out into the urethra and may block the flow of urine. The outer genitalia may show no abnormality.

Again, in analogy to the "hymen imperforatus" in women, the sacculus prostaticus, utericulus prostaticus, or vagina masculina, as it is variously named, may be closed at its urethral end. This may be associated with a cystic widening of the utricle which leads to urine retention. Such lesions are attributable to more or less slight degrees of pseudohermaphrodism.

Concerning the development of the folds in the mucosa constituting the crista urethræ, we have been able to find little or nothing. We do not know what the relationship is, if indeed there is any, between these folds and the prostatic utricle, the remains of Müller's ducts. They are said to bear some relationship to the developing prostate gland.[20]

Two principle views are presented in the literature by students of these cases. One of these is that the abnormality is due to an over-development of folds normally present in the mucosa, and no explanation is attempted of the initial stimulus to growth. Englisch is of the opinion that after the establishment of a certain grade of obstruction, the pressure of the urine exerts a continuous irritation on this region with the stimulation of epithelial growth and production of proliferative inflammatory changes which account for the gradual increase in the efficiency of the obstruction and in the gravity of the symptoms.

Posner,[21] Wilckens and especially Lederer are inclined to regard this lesion as a malformation due to arrested development. Lederer says in favor of this view that it occurs at about the point of union between the entodermal and ectodermal portions of the urethra.

Recent workers in human embryology are at variance in their views on the development of the urethral canal. Felix,[22] who writes the

20. Lowsley: Personal communication (Article in press). Am. Jour. Anat., June 15, 1912.

21. Posner: Ueber angeborene Stricturen der Harnröhre. Berl. klin. Wchnschr., 1907, xliv, 275.

22. Felix: Die Entwicklung der Harn- und Geschlechtsorgane. Handbuch der Entwicklungsgeschichte des Menschen. (F. Keibel and F. P. Mall), ii, 732.

exhaustive article on the development of the urinary and sexual organs in Keibel and Mall's system of Human Embryology, insists that the whole canal from the verumontanum to the sulcus coronarius glandis is developed from the sinus urogenitalis and is of entodermal origin. Broman,[23] on the other hand, in his recent work accepts the view that the corpus cavernosa urethræ is developed from the ectodermal or cloacal plate. Certainly this latter view would furnish the better explanation for the numerous anomalies occurring in the membranous and anterior portions of the urethra, including, perhaps, such valve-like structures as those described by Posner at the junction of the pars membranacea and the pars bulbosa. But even should we adhere to this view, the lesion we have described in the posterior urethra, is too far posterior to be ascribed to a failure in the union of entodermal and ectodermal structures. In the lack of definite knowledge we lean rather to the view that we are dealing with a simple progressive malformation and not one due to arrest of development. Certainly, the region in which this anomaly occurs is one of complex development, being the point of union of the prostatic urethra developing from the mesodermal wolffian ducts, the urethra distal to the verumontanum derived from the entodermal sinus urogenitalis, the prostatic utricle representing the remnants of Müller's ducts and the ejaculatory ducts.

CONCLUSIONS

We have been able to find no case of congenital membranous obstruction occurring in the prostatic urethra reported in full in our American literature and yet the condition has not been infrequently described abroad.

We believe that the possibility of interference with the urinary flow from such a congenital malformation should be considered whenever the cause of the obstruction is not obvious; especially should there be a persistently distended bladder. A partial obstruction of this nature is compatible with the passage of a normal daily amount of urine, but there may be either increased frequency of micturition or incontinence if the lumen is not absolutely occluded.

The condition if recognized in most instances could be easily corrected.

Autopsy findings should not be considered complete without incision through the anterior urethral wall and inspection of the complicated structures in or near the pars prostaticus.

We wish to thank Dr. Llewellys F. Barker for the privilege of reporting the case from his wards, and Mr. J. P. Webster for the excellent drawing.

23. Broman: Normale und abnorme Entwicklung des Menschen. Wiesbaden, 1911 (J. F. Bergmann), p. 476.

SUMMER DIARRHEA — HEAT — HUMIDITY *

LAWRENCE T. ROYSTER, M.D.
NORFOLK

With a literature already overcrowded with the various causes, both scientific and practical, of infant diarrhea, especially during the heated term, one is tempted to commence a paper of this character with an apology. And yet I feel that any fact which may either prove or disprove existing theories, should be set forth for the possible aid it may render other investigators along the same line.

For many years past the digestive disturbances of infants have occupied more space in our researches than all other conditions combined, and, although much has been gained and chronicled by these researches, I may safely say that up to the present moment no really definite conclusions have been reached. During all these years a large number of careful and capable students have conducted investigations on this subject, leaving in their trail almost as many theories as there were investigators, but from among all these, three have gained the most prominence, namely, milk decomposition, bacterial infection and summer heat. Two of these theories, namely, milk decomposition and bacterial infection, have been partially, if not completely, disproved as the main cause of summer diarrhea in infants, based on investigations with which you are all too familiar for me to review on this occasion. I shall therefore confine my remarks to the influence of heat, and the possible combination of humidity.

HEAT AND HUMIDITY

In looking over a vast number of statistics, gathered from all parts of the country, there has been evident a great decrease in mortality, in some cities, following a pure-milk crusade, but in this instance the fact is clearly shown that prior to such a crusade the infant death-rate was much higher than could be accounted for by climatic conditions; hence these cities can only be considered statistically since the time of the institution of milk regulation.

Taking up the question, therefore, in its relation to climatic conditions, notably heat and humidity, leaving out of consideration all other factors, we find, in brief, that our observations lead to the following superficial conclusions; that infant diarrhea, as it is commonly understood, exists practically entirely in the temperate regions, is exceedingly

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*Read in the Section on Diseases of Children of the American Medical Association at the Sixty-Third Annual Session, at Atlantic City, June, 1912.

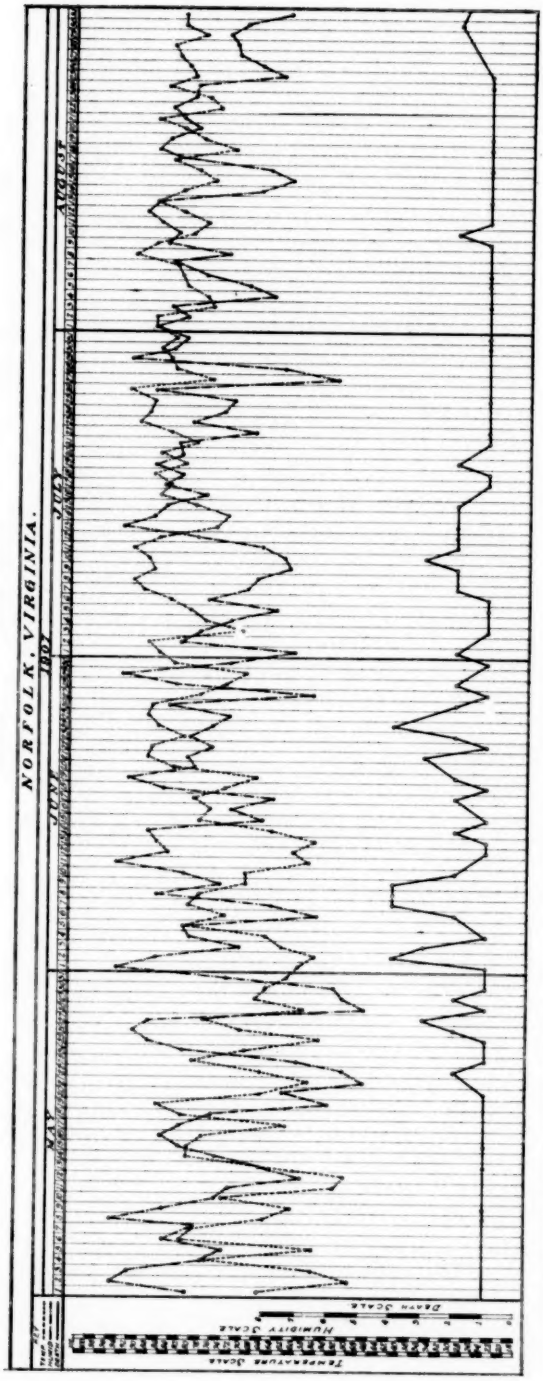

Chart 1.—Temperature, humidity and death curves in Norfolk for the months of May, June, July and August, 1907.

rare in Canada and similar countries, and equally rare in the tropics and subtropics.

The exhaustive researches of Liefmann and Lindemann, covering a period of fifteen years of daily observation in the city of Berlin, show that the death-curve, and also the sick-curve, follow an almost exactly parallel line with the 2 p. m. temperature curve. That however much the temperature may vary during the day, from early morning to late at night, the most constant guide is the 2 p. m. temperature, with which the death-curve, as I have stated, runs almost parallel. We observe, further, that in the poorer sections of the city particularly, mortality is higher among children who are deprived of out-door air; that country children are notably less affected than city children, in spite of the frequently higher temperature in the country, and that children sent to the country suffering with the condition frequently recover and recuperate very much more rapidly than those who still have to dwell in the city. Again, wherever the seaside resorts are used, or floating hospitals for the benefit of sick children, the picture is a familiar one — with what rapidity they recover and recuperate here, although the seashore may be just as hot as the city, and frequently even more humid.

It is well known that frequent bathing in cold water during the hot days, and frequent small draughts of water administered to the child, go a long way toward the prevention of summer diarrhea. And in the case of seashore and country a breeze is usually present in spite of the heat. Almost without any further argument therefore, it will be seen from these brief facts that the question largely resolves itself into one of radiation, rather than the actual instance of heat itself.

The discussion following Dr. Abt's paper at Los Angeles last year, during which remarkable statements were made by some of our friends of the far West, decided me in looking into the question of radiation still further, with the possible effect of the combination of humidity along with the heat. This latter in spite of the fact that Liefmann and Lindemann found no relation whatever between infant mortality and humidity, although they considered any humidity above 50 per cent. to be high; whereas we have very few sections of our country where the humidity is ever below 50 per cent.

There are many difficulties which present themselves in an undertaking of this kind. In studying American cities many of them are so new that records of death-rate have been kept for such a short time and are so imperfect that practically no deductions can be drawn from them. And, too, in many instances the United States Weather Bureau had been established too short a time to aid in this comparison. For no record, unless a daily one of temperature, humidity and death-rate, can give us even an approximate idea of the relations of these factors. As we

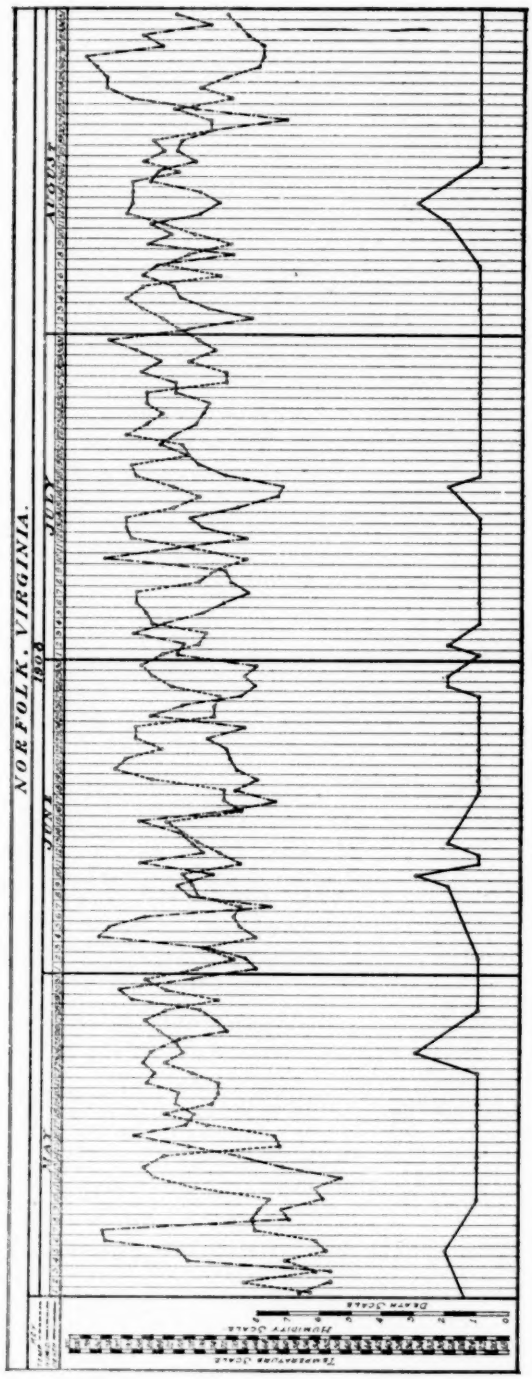

Chart 2.—Temperature, humidity and death curves in Norfolk for the months of May, June, July and August, 1908.

progress in our studies, difficulties multiply. The temperature varies in different parts of the same city, frequently as much as five, or even seven degrees, as has been shown by the German investigators above quoted, who took observations from several parts of the city, showing that in the thickly populated parts of the city the temperature was, of course, very much higher than in the suburbs, and the official weather bureau observation is always somewhat lower than that at the street level, or in other parts of the city.

The greatest difficulty in this study, however, arises from the difference between the temperature of out-of-doors and that within the dwellings, which latter is almost invariably higher, and especially in the room which, among the poor, is used as a living room and kitchen combined, where the temperature has been found to be as much as ten degrees higher than outside, thereby giving almost no possibility of radiation. Moreover, in instances where the maximum temperature in the city is registered perhaps at 2 or 3 o'clock in the afternoon, the maximum temperature in the dwellings is almost always higher during the night hours, sometimes at 8 p. m., in other instances as late as 3 the next morning. This latter emphasizes the importance of not bundling up the child too closely when it is put to bed at night, judging the necessity for bed clothing by the temperature outside of the house.

The variety of these difficulties therefore renders accurate scientific observation on the effects of climatic changes on the condition before us almost impossible. Again, the death-curve hardly gives us a fair conception of this relation, but rather would the sick-curve help us more, which, especially among the poor, where careful histories are difficult to obtain, it is practically impossible to secure. For example, where there are several sudden ascents of temperature, giving marked pinnacles in our curve, and separated by one or more days of comparatively lower temperature, it is impossible to state definitely whether the number of deaths immediately following one of these pinnacles is in reality due to the immediately preceding elevation of temperature, or to the more distant preceding one, during which the child became ill, but survived until the second or third sudden ascent immediately caused its death. These sudden rises in temperature occur more frequently during the early part of the summer, than in mid-summer, when we have a more uniform elevation of temperature. In this case the effect of the heat is rather a cumulative one, almost analogous to the cumulative effect of certain drugs. Moreover, there may develop a subacute or subchronic condition of impaired health, which the child may resist for weeks or even months, finally dying in the late summer or early autumn, in which instance the death should, in reality, be attributed to the heat of a far-preceding period. This is particularly noticeable in Norfolk, where

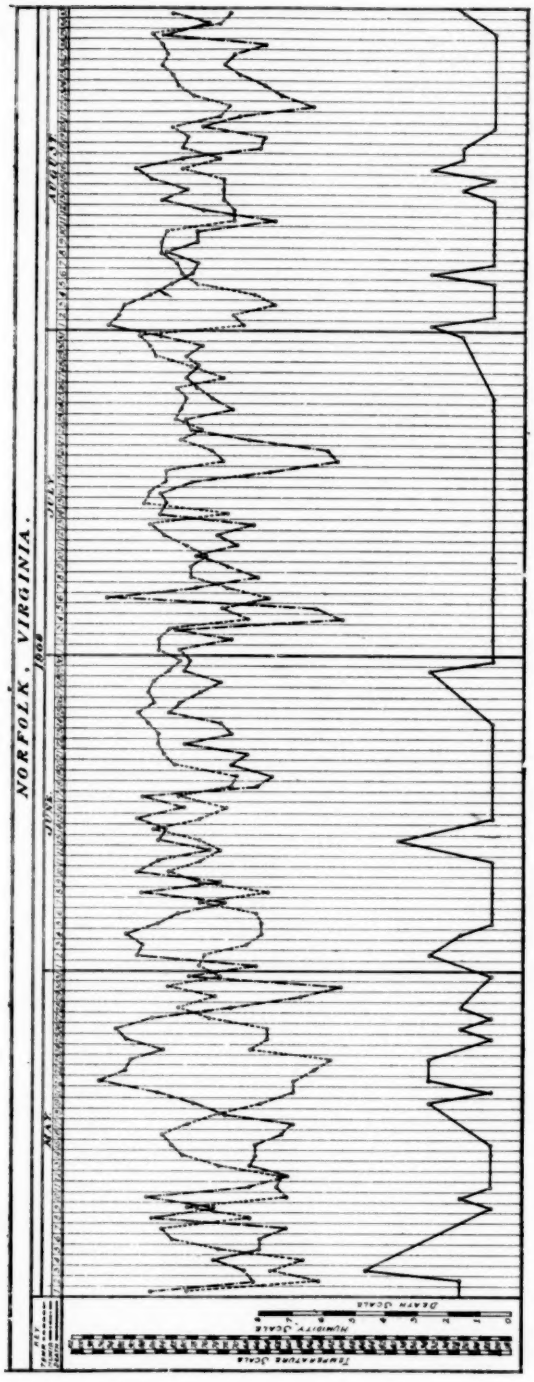

Chart 3.—Temperature, humidity and death curves in Norfolk for the months of May, June, July and August, 1909.

the large number of deaths from summer diarrhea during the early heat periods occur among the negroes, while the death-rate in the late summer shows a greater mortality among the whites. This is easily accounted for by several facts, notably the surroundings of the whites and blacks, and the superior resistance of the white stock in our city. For example, the negroes die almost as soon as they are attacked, while the whites frequently drop into a subacute or chronic state, resisting the disease for a longer period, due largely to the more intelligent care, but finally succumbing at a later period.

Considering, however, all of the difficulties, the fact is that we are at present nearer to the conception which Meinert announced to us in 1881 on heat stroke, not that the heat alone is the cause, but the heat is undoubtedly the precipitating cause, and other factors are back of it, notably the effect of artificial feeding, as among artificially-fed children the vast majority of these cases are found. The digestion of the artificially-fed child is usually taxed to its utmost by a food at best only poorly suited to its digestive powers, and no doubt the heat or lack of radiation merely precipitates the fatal condition.

In order, therefore, to investigate even superficially this question, I have gathered data from as many cities in the United States as was possible. In every instance, except that of Norfolk, I was able only to get monthly averages. Hence the curves show us comparatively little concise data. The general averages themselves are, however, exceedingly interesting. In some instances they uphold the relation between humidity and temperature, and in others they tend to disprove it. The death-rate in the following tables is for gastro-enteritis in children under 2 years of age. Taking Boston as a representative eastern city, though somewhat north of the real temperate zone, we find the following:

Boston:
Population 670,585.
Mean maximum temperature 58.
Mean minimum 42.
Average temperature 50.
Humidity 71.
Death per thousand .92.

Even a death-rate thus calculated is misleading, because the only accurate census that can be secured is that of 1910. And on this census these rates are based, because the estimated census per year is notably inaccurate. For example:

Birmingham, Alabama:
Population 132,685.
Mean temperature 63.7.
Mean humidity 78.6.
Death-rate 1.

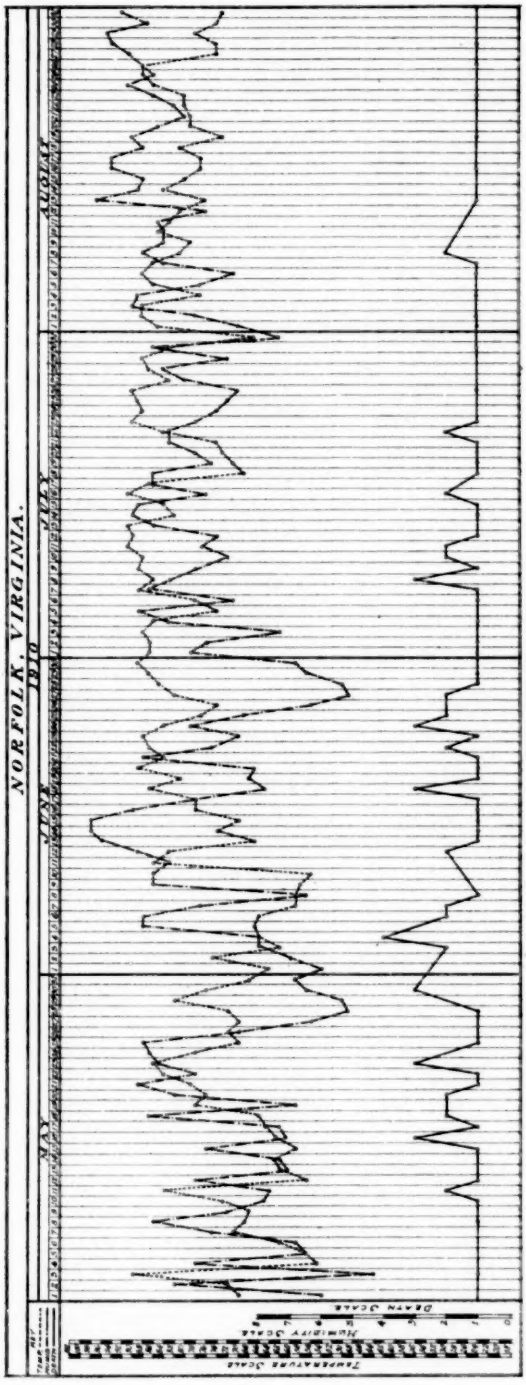

Chart 4.—Temperature, humidity and death curves in Norfolk for the months of May, June, July and August, 1910.

This is the death-rate when based on the 1910 census, but if based on the average yearly census we have a death-rate of 1.38, which is, in all probability, more nearly accurate.

Chicago, Ill.:
Population 2,185,283.
Mean temperature 50.
Mean humidity 76.
Death-rate per thousand 1.2.

Of course this does not show up clearly the sudden changes of both temperature and humidity which are known to occur in Chicago.

San Francisco:
Population 316,912.
Mean humidity 75.7.
Mean temperature 55. More or less uniform throughout the year, with practically no sudden changes. Death-rate per thousand .30.

Cleveland, Ohio:
Population 560,663.
Mean temperature 49.4.
Mean humidity 72.3.
Death-rate 1.02.

Practically all of the deaths of the year occur during July, August and September, with August as the highest point. Again this shows comparatively little, because daily records could not be secured.

Now Orleans gives us the greatest problem of all cities, as has been long recognized, the deaths here occurring on the up-grade of temperature, and not at the height as in other cities, occurring in April, which is very different from any other American city. The humidity is very nearly uniform throughout the whole year.

New Orleans:
Mean humidity 78.
Mean temperature 70.
Death-rate 1.27.

Turning, however, to San Antonio, we have a remarkable record.

San Antonio:
Population 96,000.
Maximum mean temperature 87.9.
Minimum mean temperature 52.1.
Average annual temperature 70.
Mean humidity 67.
Death-rate .49.

The temperature in San Antonio frequently reaches for an average of a whole month considerably over 100, humidity more or less uniformly low and even, and practically no exacerbation in the death-curve, with the single exception of May, 1910, for which there was no apparent cause.

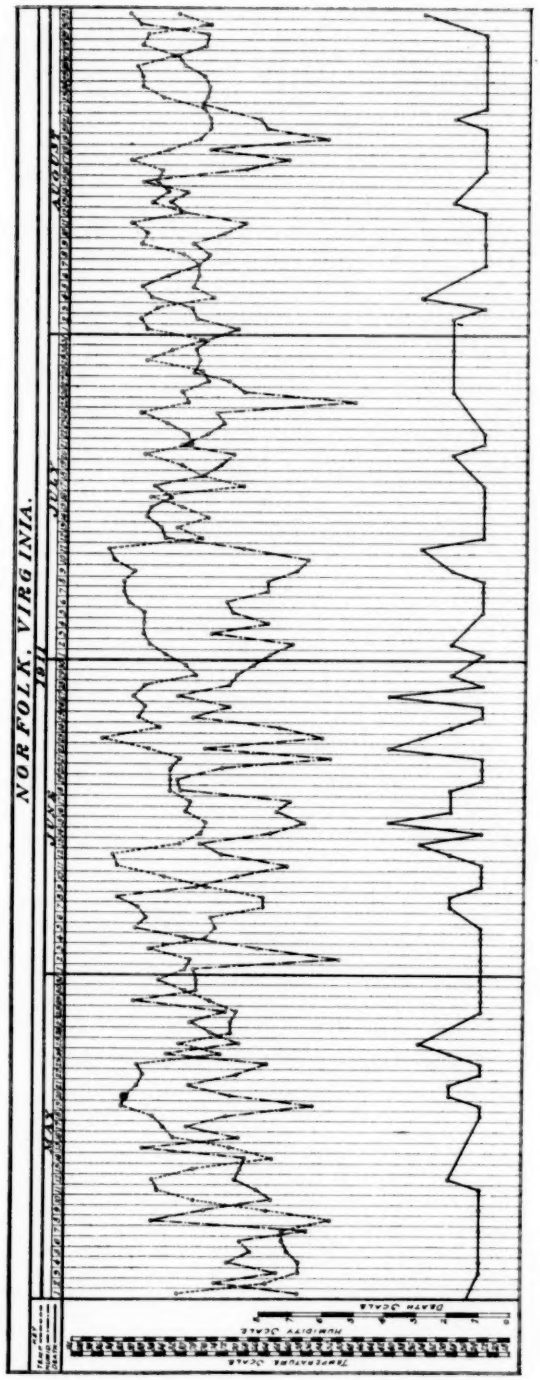

Chart 5.—Temperature, humidity and death curves in Norfolk for the months of May, June, July and August, 1911.

Denver:
Population 213,281.
Death-rate per thousand .43.
Climatic conditions are interesting.
Maximum mean temperature 63.9.
Minimum mean temperature 37.9.
Average temperature 50.9.
Mean humidity 52.3.

In Phoenix, Ariz., the statistics are drawn from a population of about 20,000. The death-rate is .60. Average maximum temperature 86, minimum 57. Humidity, 46.2. The humidity for November, December and January is rather high, which brings up the average as high as it is. The average for the rest of the year is about 35.

These records are merely interesting statistically, and give us no accurate information about the influence of sudden rises in temperature or humidity. I have, however, worked out for Norfolk a daily scale of humidity, temperature and death-rate (Charts 1 to 5) for a period of five years, and think we have a few interesting observations from this record.

Norfolk:
Population 81,000.
Death-rate per thousand 1.7.
Mean temperature 64.7.
Mean humidity 75.

The largest number of deaths in Norfolk on a single day is five, which occurred only once. A high death-rate is usually considered to be four, while two and three is about the average for high mortality. In the majority of instances where an unusual number of deaths occurs, the temperature and humidity are both well above the average, and run more or less uniformly parallel. Wherever we have an unusual number of deaths occurring on a day on which the humidity is low, we invariably have a temperature unusually high. A few examples will suffice to show these changes.

May 27, 1907, there occurred three deaths, really the first pinnacle in the curve of that year, and on this day the humidity reached 90 and the temperature 78. There was an immediate drop in the humidity, which lasted for several days, and on June 2, the death-curve reached four, while the temperature was only 57, but the humidity was 87, preceded on June 1 by humidity of 95. In this city we would hardly consider a temperature of 57 as dangerous, but the complemental relation of humidity shows up strikingly. During the next three or four days the humidity goes down to 57, while the temperature ascends rapidly to 82. The temperature remains comparatively high for the next three days, coming down on the fourth day, while the humidity again mounts to 87, during which period there are four deaths a day, again, I think, showing

a striking relation between humidity and death-rate. On June 20 the temperature reaches 84, humidity 69, with three deaths, and temperature still keeping high, humidity declining somewhat; the next pinnacle of deaths, on June 24, shows four again, illustrating the fact that although the humidity falls considerably, the temperature has soared to an unusual height. For the next several days the death-rate varies from one to two per day, until we reach July 11, when it reaches three, with a humidity of 61, unusually low for this season of the year; but on this day the temperature reaches the almost phenomenal point of 92. By this time the bulk of the mortality for our city is past, and whereas the humidity and temperature both run almost parallel, the death-rate is not particularly marked.

In the year 1908 we have only three striking pinnacles in our death curve: One on May 24, three deaths, when humidity and temperature were both high; one on June 11, with a similar condition, and one August 13, when the same number of deaths occurred, with a humidity of 76, and an unusual temperature of 92.

In May, 1909, we have the most striking pinnacle in our seriess. On May 3 we have five deaths, with a humidity of 69 and temperature of 66, but for the two days preceding this we have a temperature of 81 and a humidity of 86.

June 4, 1910, we have a death-rate reaching four, while the temperature reaches only 67, but the humidity reaches 89.

The only striking pinnacle in the Norfolk series is reached in June, 1911, when, on the thirteenth, we have three deaths; on the fifteenth, four; on the twenty-second, four; on the other days ranging from one to three. In this series we have a humidity ranging from 61 to 83, and in addition to this we have the most remarkable spell of heat known for years, running a steady upward course from 67 to 96, but marked at the pinnacles mentioned by exacerbation running as high as 96 and 97.

I have attempted no conclusion, but give out these statistics and facts merely for what they are worth, believing, however, that in a more extensive research there will be found a definite relation of humidity. The appended charts will prove of interest.

Taylor Building.

THE HYPODERMIC USE OF HEMATINICS IN THE TREATMENT OF ANEMIA IN CHILDREN, WITH REPORT OF CASES *

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The hypodermic use of medicaments calculated to make a deep and rapid impression on the blood and the blood-making organs and to combat certain infections is not new. For many years, in the treatment of secondary and tertiary syphilis, it has been the custom, originally amongst the Latins, and more latterly amongst American clinicians, to administer mercury subcutaneously. For rapidity of effect this method of giving the drug is without a peer. Of late years considerable interest has been directed toward the administration in this manner of drugs whose purpose was to overcome diseases essential to the blood itself, blood dyscrasias and blood deterioration dependent on systemic or local infection or toxemia. The old adage "remove the cause" as the primary act to be accomplished has, with reference to the treatment of many diseases, become stale and trite, and, in a vast number of instances, is more easily said than done. It becomes necessary, therefore, to combat the results of infection or toxemia by placing in the blood current substances which, if they do not destroy the circulating cause, at least mitigate its influence by supplying pabulum which continuously makes up for that which is being destroyed, thereby improving directly the quality of the blood and indirectly combating the etiologic factor.

In no class of cases do the foregoing conditions obtain with greater emphasis than in the anemias of childhood. Here the causative element, either tangible or not, is often not readily destroyed, or if it be, its by-effects remaining for some period, the indication to be met is to increase the amount of hemoglobin and the number of red cells in the blood. Aside from the administration of good food, fresh air and the improvement of environmental conditions, as is well known, the best results are obtained by the administration of so-called hematinics, of which, up to the present, iron and arsenic furnish the best examples. Both, however, interfere with digestion, and the former is absorbed with great tardiness, the largest portion of that ingested being expelled as the sulphid of iron. The latter causes nausea and diarrhea and may seriously

*Read in the Section on Diseases of Children of the American Medical Association, at its Sixty-Third Annual Session, held at Atlantic City, June, 1912.

interfere with kidney function. Thus, whatever good effect may accrue from the use of these drugs *per orem* is often lost, and at the end of a course of treatment the condition for which they were first administered may be made worse. Even in the absence of disturbing symptoms the amount which enters the circulation is infinitestimally small and the progress of the case toward recovery slow. Therefore, if these agents could be placed in the circulation with great rapidity and in sufficient amount not only to overcome the effects of the toxemia, but in slight excess of this, without disturbing the normal progress of metabolism, much in the way of a rapid upbuilding of hemoglobin and red cells could be anticipated, with a disappearance of the anemia, and, as a logical sequence, with an increase in the individual's resistance.

The results obtained by J. L. Morse,[1] detailed in a paper read before this Section in June, 1909, unquestionably prove this to be so. He employed the citrate of iron alone and noted an increase in hemoglobin. In some of his patients the effect on the erythrocytes was minus. This was not noted in my cases, probably on account of the fact that a combination of hematinics was employed, one of which was an arsenical derivative. E. S. Bullock and L. S. Peters[2] also record a successful experience with the use of the citrate of iron administered hypodermically in 256 cases of anemia secondary to pulmonary tuberculosis in adults. W. J. Barlow and R. L. Cunningham[3] treated twenty-eight patients with anemia secondary to tuberculosis and found that iron alone increased the hemoglobin, while the arsenical preparations influenced more profoundly the red cells. They also noted a marked increase in weight. Some of my cases were in adults, but they are not embraced within this report.

Before detailing my results I wish to record my experiences with this method of treatment in an attempt to define its correct status.

Much depends on the character of the preparation employed and the technic of its administration. Therefore, the selection of the preparation is of vast importance in determining the success or failure of the treatment. Strange as it may seem, citrate of iron, a substance known to consist of a definite chemical formula, possesses physical characteristics which are not always identical in samples of the drug furnished by two different pharmacists. I am not aware that the substance is allotropic, but that there exists a difference between different specimens is confirmed

1. Morse, J. L.: The Treatment of Anemias in Infancy with Citrate of Iron Administered Subcutaneously. Jour. Am. Med. Assn., July 10, 1909.

2. Bullock, E. S., and Peters, L. S.: The Use of Hypodermics of Citrate of Iron in the Secondary Anemias of Tuberculosis. Jour. Am. Med. Assn., Oct. 28, 1911.

3. Barlow, W. Jarvis, and Cunningham, R. L.: Effects of Hypodermic Injection in the Secondary Anemia of Chronic Pulmonary Tuberculosis. Jour. Am. Med. Assn., Oct. 28, 1911, p. 1435.

by the two samples which I have here, and also by the fact that the darker one is decidedly irritating, while the lighter one is free of unpleasant local effects. One specimen was prepared by a Philadelphia druggist of excellent reputation, the other by a Cincinnati chemist of equally good repute. Both of these preparations having been exposed to an equal amount of light while in my possession, the change in the one can hardly be said to be due to this factor. Bullock and Peters, while mentioning the fact that local irritation does occur, state that they did not experience it in any of their own cases and ascribe this to the fact that they employed a preparation imported from Italy. Barlow and Cunningham report induration in all their cases which were treated with iron citrate alone, while sodium cacodylate produced none. In my earlier cases I employed 3/4 of a grain of citrate of iron, as recommended by Morse, but subsequently found 3/10 of a grain to be as efficient and without systemic toxic effect. As the majority of the patients in my cases here reported exhibited more or less deficiency in the number of red cells, as well as in the percentage of hemoglobin, I have made use of the following combination, unless for some reason, as kidney disease, I have felt that arsenical preparations were contra-indicated:

℞		gm. or c.c.
Ferri citratis	gr. 3/10 or ¾	0.018 or 0.045
Sodii cacodylatis	gr. ½	or 0.03
Sodii glycerophosphatis	gr. 1½	0.09
Aquæ destil (Sterile)	mxx	1.30

This appears to have a more rapid and certainly a broader effect than the citrate alone. It is non-irritating and the subjective tonic effect is quickly experienced, this being especially mentioned by adult patients.

TECHNIC

The technic of administration may make for or mar the success of an individual case. An ordinary hypodermic syringe, preferably all glass, is employed. Of course sterilization of the needle and syringe and antisepsis of the site of injection are to be enforced. An ordinary steel needle may be employed if it be washed out with alcohol immediately after use. A gold needle will not rust at all. Platinum needles, I have found to be too soft; they bend and break readily and are expensive to replace. The injection is to be given deep. The needle is held at right angles to the point of injection; it is then quickly plunged to its full length into the underlying tissues. After experimenting on several portions of the body I find that the postero-lateral inner aspect of the upper portion of the arm furnishes the best and least painful site for the injection. The tissues here are loose and readily adapt themselves to the small amount of fluid placed within them.

If the injection be properly made in the majority of instances there will be no pain and no local reaction. The most that is complained of is a slight stinging sensation as the fluid enters the tissues. This may be momentarily severe if a nerve filament be pierced or pressed on. It rapidly subsides, however. There is left behind no soreness, no induration and no abscess-formation. If, however, the fluid be not placed sufficiently deep or some of it enters between the layers of the skin, the local reaction is severe and manifests itself by great pain, swelling, redness which may extend for some distance and induration, which remains over a long period of time. Not infrequently these areas of induration are preceded by severe ecchymoses. I have never encountered abscess-formation. The only accident which I have encountered was in a very nervous child who, in jerking away after the needle had been inserted in the arm, caused the needle to break off *in situ*. It was removed without difficulty at once under cocain and aside from the momentary embarrassment caused no inconvenience.

Systemically there are no immediate effects, unless a dose too large for the individual be given. Under the latter circumstances the following symptoms, as experienced by myself from a dose of gr. 1½ of citrate of iron self administered, may be noted in children or complained of in adults: From two to three minutes after injection there occurs intense vertigo, a feeling of nausea which may proceed to vomiting, a sensation of faintness and weakness, trembling of the legs and arms, cardiac palpitation, increase in the pulse, which becomes small, and the body is bathed in a cold perspiration. After reclining, all these symptoms pass gradually away within fifteen to twenty minutes. Young infants frequently vomit from a dose which is too large for the individual. Likewise the symptoms just detailed may not occur until after several injections are given, each individual injection being free of symptoms, showing that the action of the iron citrate is cumulative. I have noted these symptoms appear toward the end of a course of treatment when the blood picture was normal or much improved and the patient manifested every sign of good health. I have taken this as a sign to discontinue treatment. If the dose be within the maximum for the individual, and this must be determined in each case, it being quite safe to begin with ¾ of a grain, there are no systemic ill effects. The only effects are good. The patient's appetite speedily improves, the color is bettered, languor and apathy are replaced by buoyancy and an eagerness for play, and adults note a sensation of revivification, usually voluntarily expressed. These subjective sensations readily find a substantial basis for their existence in a speedy improvement of the quality of the blood. The hemoglobin is rapidly increased and the red cells as well.

In some cases wherein the hemoglobin was materially increased Morse noted a reduction in the number of red cells. In my own series this occurred in but one instance.

The following cases represent the cases in children occurring in my own practice which I have treated within the past three years. Complete blood counts were made in all cases. My report includes twenty cases in children. Although more were treated, this number was regarded as sufficient to illustrate the value of the treatment.

CASE REPORTS

CASE 1.—Z. H., female, aged 12 years. Chlorosis.

June 23, 1909:

Hemoglobin	63%
Erythrocytes	4,240,000
Leukocytes	7,000
Color index	.74

Achromocytosis and poikilocytosis, present.

Polymorphonuclears	68%
Small lymphocytes	24%
Large lymphocytes	6.5%
Eosinophils	1.00
Basophils	.5

Eight injections.

July 28, 1909:

Hemoglobin	89%
Erythrocytes	4,320,000
Leukocytes	7,200
Color index	.92

Blood normal in appearance.

CASE 2.—B. G., female, aged 14 years. Chronic parenchymatous nephritis.

July 3, 1909:

Hemoglobin	55%
Erythrocytes	4,950,000
Leukocytes	10,800
Color index	.55

Six injections of ferri citratis, gr. 3/5.

July 12, 1909:

Hemoglobin	60%
Erythrocytes	5,410,000
Leukocytes	9,400
Color index	.55

Nine injections.

Nov. 9, 1909:

Hemoglobin	87%
Erythrocytes	4,790,000
Leukocytes	8,400
Color index	.87

CASE 3.—A. E., female, aged 3 years. Inherited syphilis; general adenopathy.

July 3, 1909:

Hemoglobin	56%
Erythrocytes	3,000,000
Leukocytes	10,000
Color index	.93
Polymorphonuclears	50%
Small lymphocytes	42%
Large lymphocytes	6%
Eosinophils	2%

Stained specimen shows general achromocytosis, microcytes, macrocytes.

Mercurial inunctions and nine injections.

Sept. 5, 1909:

Hemoglobin	83%
Erythrocytes	4,200,000
Leukocytes	9,800
Color index	.98

CASE 4.—E. O., female, aged 4 years. Cyclic vomiting; acetonuria.

Aug. 3, 1909:

Hemoglobin	62%
Erythrocytes	240,000
Leukocytes	8,200
Color index	1.29
Polymorphonuclears	72%
Small lymphocytes	20%
Large lymphocytes	9%

Six injections.

Sept. 7, 1909:

Hemoglobin	78%
Erythrocytes	3,230,000
Leukocytes	8,500
Color index	1.20

Seven injections.

Oct. 8, 1909:

Hemoglobin	87%
Erythrocytes	4,190,000
Color index	1.03

CASE 5.—E. R., female, aged 14 years. Rapid growth in past six months. Menstruated once. Languor, anorexia, pica.

Oct. 25, 1909:

Hemoglobin	64%
Erythrocytes	3,921,000
Leukocytes	6,800
Color index	.81
Polymorphonuclears	53.7%
Small lymphocytes	28.8%
Large lymphocytes	13%
Eosinophils	4.44%
Basophils	.06%

Erythrocytes have pale centers, few macrocytes, numerous microcytes, occasional poikilocytes.

Six injections.

Nov. 4, 1909:

Hemoglobin	81%
Erythrocytes	4,410,000
Leukocytes	8,900
Color index	.91
Polymorphonuclears	66%
Small lymphocytes	26%
Large lymphocytes	7%
Eosinophils	1%

Red cells still visibly deficient.

Seven injections.

Nov. 28, 1909:

Hemoglobin	88%
Erythrocytes	5,290,000
Leukocytes	7,800
Color index	.84

Red cells normal in every respect.

Total number of injections 13.

CASE 6.—K. McD., female, age 12. Very studious, choreic, constipated, anorexia, indicanuria.

Nov. 4, 1909:

Hemoglobin	70%
Erythrocytes	4,240,000
Leukocytes	68,000
Color index	.84

Achiomocytosis general, many microcytes, few poikilocytes.
Polymorphonuclears 51%
Small lymphocytes 13%
Large lymphocytes 28%
Eosinophils 6%
Basophils 2%
Eight injections.

Nov. 31, 1909:
Hemoglobin 82%
Erythrocytes 4,800,000
Leukocytes 7,200
Color index ..... .85
Achromocytosis present, but less marked. Microcytes less, few poikilocytes.

CASE 7.—A. D., female, aged 10. Just recovered from post-scarlatinal nephritis.

Nov. 12, 1909:
Hemoglobin 69%
Erythrocytes 3,982,000
Leukocytes 7,800
Color index ..... .87
Decided achromocytosis.
Polymorphonuclears 53%
Small lymphocytes 33.6%
Large lymphocytes 13.0%
Eosinophils 2%
Basophils 2%
Nine injections.

Dec. 18, 1909:
Hemoglobin 86%
Erythrocytes 4,310,000
Leukocytes 7,600
Color index ..... .99
General appearance of blood quite normal.

CASE 8.—I. B., male, aged 4 weeks. Sepsis neonatorum, wasted; metastatic abscess.

April 28, 1910:
Hemoglobin 30%
Erythrocytes 1,330,000
Leukocytes 13,000
Color index 1.12
Five injections.

May 6, 1910:
Hemoglobin 38%
Erythrocytes 1,600,000
Leukocytes 14,000
Color index 1.18
Died of general sepsis.

CASE 9.—B. L., female, aged 13. Rheumatic purpura.

Aug. 5, 1910:
Hemoglobin 60%
Erythrocytes 4,100,000
Leukocytes 14,000
Color index ..... .73
Achromocytosis, microcytes and poikilocytes present.
Polymorphonuclears 65%
Small lymphocytes 24%
Large lymphocytes 8%
Eosinophils 3%
Fourteen injections.

Sept. 6, 1910:

Hemoglobin	90%
Erythrocytes	4,500,000
Leukocytes	12,000
Color index	.88

CASE 10.—A. H., male, aged 6 years. Cyclic vomiting.

Aug. 31, 1910:

Hemoglobin	60%
Erythrocytes	3,600,000
Leukocytes	16,000
Color index	.83
Polymorphonuclears	68%
Small lymphocytes	23%
Large lymphocytes	7%
Eosinophils	2%

Seven injections.

Oct. 2, 1910:

Hemoglobin	83%
Erythrocytes	4,200,000
Leukocytes	11,000
Color index	.98

CASE 11.—A. S., female, aged 13 years. Acute articular rheumatism; rheumatic endocarditis of mitral valve.

Sept. 22, 1910:

Hemoglobin	40%
Erythrocytes	3,800,000
Leukocytes	7,600
Color index	.52
Polymorphonuclears	68%
Small lymphocytes	22%
Large lymphocytes	8%
Eosinophils	2%

Red cells quite uniformly deficient in hemoglobin.
A few microcytes and poikilocytes present.
Nine injections.

Nov. 18, 1910:

Hemoglobin	85%
Erythrocytes	4,300,000
Color index	.9

General appearance normal.

CASE 12.—A. H., male, aged 3 years. General adenopathy and objective pallor.

Oct. 13, 1910:

Hemoglobin	58%
Erythrocytes	2,900,000
Leukocytes	14,000
Color index	1.00
Polymorphonuclears	62%
Small lymphocytes	26%
Large lymphocytes	11%
Eosinophils	1%

Microcytes, macrocytes, poikilocytes present; eight injections.

Nov. 9, 1910:

Hemoglobin	80%
Erythrocytes	4,200,000
Leukocytes	11,600
Color index	.92
Polymorphonuclears	65%
Small lymphocytes	28%
Large lymphocytes	5%
Eosinophils	2%

Jan. 15, 1911: Just recovering from an attack of double otitis media and acute non-suppurative cervical adenitis.

Hemoglobin	48%
Erythrocytes	3,600,000
Leukocytes	6,200
Color index	.66

Seven injections.

Feb. 18, 1912:

Hemoglobin	82%
Erythrocytes	4,300,000
Leukocytes	6,300
Color index	.93

CASE 13.—B. H., female, aged 9 years. Nervous, anorexia.

Jan. 15, 1911:

Hemoglobin	72%
Erythrocytes	2,810,000
Leukocytes	9,000
Color index	1.28

March 5, 1911:

Hemoglobin	78%
Erythrocytes	2,900,000
Leukocytes	8,400
Color index	1.39

Total number of injections three. Discontinued treatment on account of nervousness.

CASE 14.—Baby P., male, aged 9 weeks. Malnutrition; gastro-intestinal catarrh; pertussis.

Feb. 9, 1911:

Hemoglobin	31%
Erythrocytes	2,600,000
Leukocytes	4,600
Color index	.69

Achromocytosis, microcytes, poikilocytes present.
Twelve injections.

March 5, 1911:

Hemoglobin	49%
Erythrocytes	3,100,000
Leukocytes	7,200
Color index	.79

Achromocytosis, microcytes and poikilocytes present.
General condition much improved.

CASE 15.—E. G., female, aged 13 years. Chlorosis.

Feb. 15, 1911:

Hemoglobin	64%
Erythrocytes	4,140,000
Leukocytes	8,400
Color index	.74

Achromocytosis marked.

Polymorphonuclears	49%
Small lymphocytes	37%
Large lymphocytes	13%
Eosinophils	1%

Seven injections.

March 18, 1911:

Hemoglobin	85%
Erythrocytes	4,300,000
Leukocytes	8,500
Color index	.98

Red cells appear healthy.

CASE 16.—Baby C., aged 10 months. Malnutrition; scurvy.

April 8, 1911:

Hemoglobin	40%
Erythrocytes	3,100,000
Leukocytes	8,000
Color index	.64
Polymorphonuclears	68%
Small lymphocytes	22%
Large lymphocytes	10%

Six injections.

April 27, 1911:

Hemoglobin	65%
Erythrocytes	4,000,000
Leukocytes	8,200
Color index	.81

Six injections.

May 10, 1911:

Hemoglobin	80%
Erythrocytes	4,250,000
Leukocytes	9,800
Color index	.94

Total number of injections twelve.

CASE 17.—S. L., female, aged 12 years. Furunculosis; chlorosis.

Jan. 17, 1911:

Hemoglobin	69%
Erythrocytes	3,900,000
Leukocytes	14,000
Color index	.88

Achromocytosis.

Polymorphonuclears	74%
Small lymphocytes	18%
Large lymphocytes	7%
Eosinophils	1%

Treated with stock vaccines, Brewer's yeast, followed by six injections.

March 5, 1911:

Hemoglobin	76%
Erythrocytes	4,100,000
Leukocytes	12,000
Color index	.90

Same treatment. Six injections.

April 9, 1911:

Hemoglobin	85%
Erythrocytes	4,420,000
Leukocytes	10,000
Color index	.96

CASE 18.—M. B., female, aged 9 years. Chorea, rheumatic endocarditis of mitral valve.

Aug. 16, 1911:

Hemoglobin	68%
Erythrocytes	3,800,000
Leukocytes	12,600
Color index	.9
Polymorphonuclears	68%
Small lymphocytes	23%
Large lymphocytes	8%
Eosinophils	1%

Complete recovery after three months' rest in bed.

Nine injections after acute symptoms subsided.

Dec. 1, 1911:

Hemoglobin	85%
Erythrocytes	4,200,000
Leukocytes	8,000
Color index	1+

CASE 19.—J. H., female, aged 6 years. Chronic gastro-intestinal indigestion, night terrors, lithuria, indicanuria, chlorotic type of blood.

Jan. 21, 1912:

Hemoglobin	71%
Erythrocytes	4,100,000
Leukocytes	6,200
Color index	.86
Polymorphonuclears	62%
Small lymphocytes	27%
Large lymphocytes	11%

Treated 1 month, eight injections.

April 27, 1912: After attack of varicella.

Hemoglobin	82%
Erythrocytees	4,100,000
Leukocytes	7,200
Color index	1.00

CASE 20.—S. S., male, aged 5 years.

March 20, 1912:

Hemoglobin	60%
Erythrocytes	3,500,000
Leukocytes	7,300
Color index	.88
Polymorphonuclears	63%
Small lymphocytes	23%
Large lymphocytes	13%
Eosinophils	1%

Fourteen injections.

April 25, 1912:

Hemoglobin	85%
Erythrocytes	4,200,000
Leukocytes	7,900
Color index	1+

In all, 202 injections were given. All patients, save Case 19, received the combination of hematinics originally stated. In Case 19, because of the kidney lesion, the patient received ferri citratis gr. ¾ alone. The average number of injections to a case was a little over ten. The highest number of injections given in a single case was fifteen. In Case 13 the patient received the lowest number, three injections. All of the patients were rapidly benefited by treatment, except in Cases 8, 13 and 14. In Case 8 the condition was hopeless from the beginning, the infant, 4 weeks old, succumbing to general sepsis and metatastatic abscesses. Even in this patient, however, the five injections given raised the hemoglobin from 30 per cent. to 38 per cent. in one week. The patient in Case 13 reported irregularly for treatment, and while showing a very slight increase in hemoglobin and red cells, remained practically unchanged. In Case 14 the patient received regular and continuous treatment, but showed very little improvement. The infant throughout the course suffered from chronic gastro-intestinal indigestion and nearly died of pertussis and

bronchopneumonia. At the age of over two years the mother writes me from New York that its physical condition is very good.

In Case 12 the patient received fifteen injections over a period of four months and illustrates well the tonic effect of the treatment. In a little less than one month after eight injections his hemoglobin rose from 58 per cent. to 80 per cent., and his red cells from 2,900,000 to 4,300,000. A severe attack of non-suppurating, but lingering bilateral cervical adenitis and double otitis media reduced this again to 48 per cent. hemoglobin and 3,600,000 red cells. Seven injections in a little over four weeks brought them up again, respectively, to 82 per cent. and 4,300,000.

CONCLUSIONS

1. In the hypodermic injection of hematinics we possess a quick, safe and reliable means of treating the anemias of childhood.

2. A combination of iron and arsenic compounds seems to have a better effect than either alone.

3. Small doses of each give as good results as large ones.

4. The tonic effect is noted almost immediately after beginning treatment.

5. The injections should be made deep in loose tissue.

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PELLAGRA IN CHILDREN *

(A PRELIMINARY REPORT)

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Pellagra has existed for any length of time on the North American continent only in Mexico. Since 1864, cases of the disease have from time to time been reported in the United States. Except for a few sporadic cases, however, it is doubtful if pellagra was existent in this country prior to the year 1900. In the fall of 1906, an increasing number of puzzling cases developed at the Mount Vernon (Ala.) Asylum for insane negroes. A few such cases had been observed in the institution since the summer of 1901, but were diagnosed no more definitely than cases of "marked general debility." The rapid spread of the malady aroused the institutional authorities to a more zealous study of the disease for the purpose of control.

Dr. G. H. Searcy, assisted by Dr. Isadore Dyer, New Orleans, and Drs. McCafferty and Somerville, Mt. Vernon, worked out these cases, eighty-eight in all, and reported them as pellagra at the meeting of the State Medical Association of Alabama, April 19, 1907. Important and significant facts brought out in this study were as follows:

1. More than 90 per cent. of the cases were in females.

2. No nurse contracted the disease. The nurses' association with the inmates were very close, handling them frequently and sleeping in halls adjoining and opening into their rooms; living, altogether, very much the same life except in regard to diet.

3. The main article of diet with the inmates was corn bread. The nurses ate biscuits and light bread and had a more varied diet. A sample of the meal used was examined by a government expert and was found to be moldy, full of fungi and bacteria.

4. The spread of the disease was immediately checked when the corn bread diet was changed. For test purposes eight inmates, apparently free from symptoms at the beginning of the test, were kept on bread made from the meal examined. One of these very shortly developed pellagra, another began to show symptoms, and all displayed so rapid a decline in health that the experiment was discontinued.

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*Read in the section on Diseases of Children of the American Medical Association at the Sixty-Third Annual Session, Atlantic City, June, 1912.

These findings are given in some detail for two reasons: (1) Searcy's report, which contained a warning to physicians in the south to be on the lookout for the disease, did not attract the attention it so richly deserved; (2) the findings conform closely to observations made by many previous writers in Europe and by later writers in the United States.

In the same year, 1907, but working independently, Dr. J. W. Babcock reported the existence of pellagra among the inmates of the State Insane Asylum at Columbia, S. C.

Babcock has made some excellent studies on the disease. He deserves especial credit for creating a widespread interest in pellagra and for provoking others to give to the subject serious thought and study.

The United States Public Health and Marine-Hospital Service early had men in the field making extensive and intensive studies. The men in this service have done much to promote educational work on pellagra. They are liberal contributors to the symposia on the subject, without which for several years past no medical meeting in the southern states has been regarded as complete.

The disease is now readily recognized and is promptly reported whenever it makes its appearance in a new community.

Medical journals are devoting much space to the discussions on pellagra; the Public Health and Marine-Hospital Service has issued some valuable bulletins and publications; several text-books by American authors have been placed on the market; the literature on the disease in this country is becoming voluminous.

A review of the literature, carefully selected but comprehensive, reveals the following to be some of the more important findings relative to pellagra as it exists in the United States:

1. The disease is spreading with startling rapidity.

2. More females than males contract the disease.

3. The disease is not contagious.

4. No age is exempt, but young adults between 30 and 40 years seem to be slightly more susceptible.

5. Pellagra attacks both whites and blacks and in about the same proportion. Jews apparently enjoy immunity.

6. Occupations requiring indoor life seem to favor its development.

7. Pellagra occurs more frequently in the rural population than in the population of cities. On the other hand, it is met with more commonly in penitentiaries, insane asylums, orphan asylums, mining camps, cotton mills and factory villages, etc., than in the country.

8. Pellagra, as a rule, is found amidst insanitary conditions. It occurs, too, in homes which in themselves are of good sanitary and

economic condition, but which adjoin some mining camp or mill village in which the disease exists. Again, breaking all rules, it attacks, not infrequently, the well-to-do city dweller, living under modern hygienic conditions.

9. Any ailment causing a run-down condition predisposes to pellagra. The disease is so commonly met with in persons infected with hookworm or ameba that some investigators have convinced themselves of a direct causal relation between pellagra and these intestinal parasites. Pellagra frequently develops after pregnancy, prolonged lactation, tuberculosis, typhoid fever, etc. Alcoholics are more susceptible than persons of temperate habits.

10. Pellagra favors the warmer climates of the southern states.[1] It is much influenced by season. New outbreaks invariably occur in the spring or summer months. Symptoms in pellagrins are much relieved and often disappear in cold weather, only to reappear the following spring. Symptoms, especially of the skin, are aggravated by exposure to the sun's rays.

11. The cause of pellagra is still unknown. It has been observed that pellagra made its appearance in the south, where cornmeal has been a popular article of diet for many years, about the time the corn crops in this section of the country became insufficient to supply the demand, and when shipped meal of an inferior quality came into general use.

That pellagra is in some way connected with the use of corn as an article of diet is an opinion almost as old as the disease itself. The entrenchment of this idea in the minds of a majority of those connected with the study of pellagra has been repeatedly and often brilliantly assailed. In support of Sambon's theory that pellagra is a parasitic disease transmitted by the buffalo gnat, it has been observed that in this country, too, many houses and villages in which pellagra exists are situated near to running streams or branches, in some of which, at least, the larva of *Simulium* has been looked for and found; and that in its behavior the disease suggests itself as being one of place and locality.

The idea, however, that pellagra is a food-poisoning, in some way connected with the use of corn as an article of diet, is still the dominant one. This fact alone does not make that idea right. While theories continue to multiply, opportunity yet remains for some medical worker in the United States to demonstrate the real cause of the disease.

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1. Swan, *Southern Med. Jour.*, July, 1911, has pointed out the fact that there are probably many cities and localities outside the lower austral zone which have a sufficient maximum temperature for a part of the year, and a sufficient total heat to fulfill the requirements essential for the development of the so-called tropical and semi-tropical diseases.

12. The last finding of this review was that data relating to pellagra in children is, in this country, very meager. With but few exceptions no case reports of this disease in children have been published. The few cases in print have been brought out to illustrate some phase, other than the possible modifications of the disease in children.

Aside from the mere mention of the fact that young infants and children may be attacked, scant attention has been given to the pellagra of childhood.

It was this finding that prompted me to undertake the paper in hand, not so much with the expectation of adding to the literature anything which in itself would be regarded as valuable, but with the hope of suggesting a profitable line for fuller investigation.

The data in the study to follow was accumulated from three of my own cases, from personal interviews and from replies to letters addressed by me to sixty physicians, who for the most part have had wide experience with pellagra. The questions contained in the letter were as follows:

1. Age of youngest child in which you have observed undoubted pellagra?

2. Age of youngest child in which you suspected, but were unable to positively diagnose, pellagra?

3. What proportion of your pellagra cases have been children under fifteen years of age?

4. What differences, if any, have you noted in the symptoms of pellagra in children and in adults?

5. What difference, if any, in the mortality?

6. Do you regard heredity as an etiologic factor? Why?

7. Have you any evidence that the disease can be carried from mother to child through the agency of the mother's milk? Any contra-evidence?

Forty-eight replies were received. Fifteen, however, replied that they had not encountered pellagra in children. Two of the fifteen were superintendents of institutions in which the inmates were all adults. Five out of eight pediatric men who were written to, had not met with the disease in children; of the remaining number who had not encountered the disease in children, seven live in good-sized towns or cities. Only one lives in a small country town. The combined cases seen by eight pediatric men, all living in cities, number only six. Five of these cases, to my knowledge, were referred from either the country or a village to the city for treatment. These facts very strongly suggest that city children enjoy immunity to a considerable degree.

The answers to Question 1 regarding the youngest age at which undoubted pellagra was observed were as follows:

2 months, age given by 1 correspondent.
4 months, age given by 1 correspondent.
5 months, age given by 1 correspondent.
6 months, age given by 2 correspondents.
15 months, age given by 1 correspondent.
18 months, age given by 1 correspondent.
2 years, age given by 7 correspondents.
3 years, age given by 5 correspondents.
4 years, age given by 2 correspondents.
5 years, age given by 3 correspondents.
6 years, age given by 2 correspondents.
7 years, age given by 1 correspondent.
8 years, age given by 1 correspondent.
10 years, age given by 1 correspondent.
13 years, age given by 1 correspondent.
14 years, age given by 1 correspondent.

Two correspondents reported having met with the disease in children, but had kept no record of their ages.

It is seen that while pellagra may occur in the very youngest infant, it is met with much more frequently after the eighteenth month.

In reply to Question 2, as to the age of the youngest suspected case, twenty answered that no unconfirmed cases of the disease in children had been seen by them. Six either did not answer or answered in such a way as to indicate that the question was not understood. Five answered as follows:

1. Youngest suspect, 9 months. Gave age of youngest undoubted case, 2 years.
2. Youngest suspect, 12 months. Gave age of youngest undoubted case, 3 years.
3. Youngest suspect, 18 months. Gave age of youngest undoubted case, 3 years.
4. Youngest suspect, 2 years. Gave age of youngest undoubted case, 4 years.
5. Youngest suspect, 9 years. Gave age of youngest undoubted case, 3 years.

The question was put for the purpose of eliciting information as to whether in young infants and children, modifications of symptoms sufficient to prevent ready recognition occurred with such frequency as to demand consideration.

Personal experience is at variance with the twenty who answered that no unconfirmed cases had been observed. I have seen one girl 20 months old, and another girl 11 years old, in both of whom I strongly suspected pellagra, and in neither of whom was I able, after exhausting all procedures of elimination known to me, to fix the diagnosis on pellagra or on anything else.

This experience induces me to attach more weight to the answers of the five, who have had suspected cases, than their number may justify. The personalities back of the five answers, however, add weight. Each represents an individual of prominence in the medical world. Some significance, to my mind, attaches itself to the fact that four out of the five suspected patients were younger than the youngest undoubted pellagra patient observed by the respective correspondent. Time for further investigation on this phase of the study is desired.

To Question 3, as to the proportion of children among their pellagra cases, twenty-two answered definitely. The lowest was 1 per cent., the highest was 50 per cent. The average for the twenty-two being 10.5 per cent. A conservative estimate would be that about 10 per cent. of all pellagrins are children under 15 years of age.

To Question 4, regarding symptoms, only three out of thirty-three failed to reply. Thirteen had noted no symptoms in children differing from the symptoms in adults. Seventeen had noted more or less differences. Fifteen of the seventeen agreed that the nervous symptoms in children were less marked than in adults. Three limited the differences between the child type and the adult type of the disease to the nervous symptoms. Five said the disease ran a more acute course in children, but with generally milder symptoms. One of this group of five said that the intestinal symptoms in young children were sometimes more troublesome than in adults. Seven emphasized the fact that the symptoms in children were "very much more mild." One said the symptoms in children were worse than in adults. One said the symptoms were classical in children except for a special tendency to intestinal derangement of severe nature.

Between the group embracing those who observed no differences in symptoms and those who regarded the symptoms as worse in children on the one hand, and the group embracing all those who saw more or less marked differences in favor of children, on the other hand, it is to be regretted that a comparative study cannot be made from the standpoint of the number of cases observed by respective groups. When given the proportion of pellagrous children observed was considerably less with the former than with the latter group. With the pictures of three cases personally studied and the letters received from a number of able workers before me, I am convinced that marked nervous symptoms in pellagrous children are not commonly met with; that frequently the nervous symptoms are not in evidence at all in such cases; that as a general thing the symptoms of pellagra in children, with the possible exception of the eruption, are not so well marked as in the adult; and that not uncommonly, the eruption may be the only symptom prominently manifest.

From a letter recently received from Dr. E. M. Mason, Birmingham, Ala., who has seen an unusual number of both adult and juvenile pellagrins, the following is quoted:

> I have seen probably twenty cases of pellagra in children under 12 years of age. In all the cases, the skin symptoms were prominent, and more so than other signs. All the children were well nourished, seemed not to feel badly, and complained very little. Diarrhea and nervous symptoms were not pronounced.

The above description fits the three cases observed by me. These children played and seemed to enjoy life as fully as any normal child.

One of the three was a negro boy 5 years old, who was seen in the second summer of his attack. His body was fairly well nourished, his appetite was good, he slept well, did not complain of pain, but did, at times, complain of being tired and would not play like other children. His mind was bright and no nervous symptoms at all were in evidence. The eruption on hands, neck and feet was typical.

The other two cases were little girls. One was seen in the fall after the eruption had persisted all summer; the other was seen for the first time by me three weeks prior to this report, just ten days after the eruption appeared. Except for a sore mouth in the first girl and for their eruptions, both apparently enjoyed good health.

In answer to Question 5, nineteen regarded the mortality in children as less than in adults, ten of the nineteen answering "much less in children." Seven regarded the mortality as being about the same. One said it was higher in children. Six did not answer.

To Question 6, regarding heredity, all answers but six were negative. These six expressed the opinion that heredity should be considered, but only in so far as a weakened constitution inherited from pellagrous parentage might predispose to the disease.

Unfortunately Question 7 was not added to the letter form until the study had progressed for some time. Only eleven replies containing data on this point were received. Nine had seen pellagrous mothers, who had been or were nursing infants without any evidence of the disease being manifest in the latter. Although the number of infants so observed was not given in all of the nine answers, at least thirteen babies are here represented.

The youngest pellagrin reported to me, 2 months old, nursed a pellagrous mother for four weeks. The baby was then fed on malted milk. The mother died of pellagra when the infant was six weeks old. "The erythematous rash did not appear until several days after the mother's death, but I was informed by the midwife who attended the mother that the infant was much emaciated at birth and had been affected with a profuse, foul-smelling diarrhea since one week old.[2]

The above case presents several interesting problems. Was pellagra contracted in utero? Was it transmitted through the mother's milk? or was it contracted in neither way, but through some other agency? While these questions are worthy of consideration, until further data is forthcoming, speculations would add length but not depth to the study in hand.

Another reported three infants dying while nursing pellagrous mothers. He did not know whether these infants had pellagra or not. He attended none of them, but he was reliably informed that all three had bowel disorders.

2. Letter received from Dr. T. C. Savage, Jefferson, Alabama.

I regret that I have not sufficient data in hand to justify my position in insisting that the infant should not be permitted to nurse the pellagrous mother. Certainly the possibility of transmitting the disease in this way has not been disproved. On the other hand, can the pellagrous mother or any mother whose constitution is overwhelmed with disease, give a milk suitable for the nourishment and the development of her infant? It ought to be readily admitted that the tax on her system incident to lactation would unfavorably influence the prognosis of the pellagrous mother's own case.

In closing I would respectfully request all those in possession of any data that might throw light on the points brought out in this paper to kindly submit them to me for a future and a more elaborate report.

Woodward Building.

PROGRESS IN PEDIATRICS

THE WASSERMANN-NEISSER-BRUCK REACTION *

PROF. DR. A. JESIONEK
GIESSEN

ABSTRACTED BY HARVEY PARKER TOWLE, M.D.
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Jesionek has published a critical review of the literature on the subject of the Wassermann reaction in syphilis which is unusually complete in extent and judicial in tone. The discovery of the *Treponema pallida* was followed so soon by the publication of Wassermann's serologic method of diagnosis and the latter so quickly by Ehrlich's method of chemotherapy that the intervals were too short to allow the study of any to be completed before the interest of the medical public was attracted to its successor. This diversion of attention has particularly followed Ehrlich's discovery. The interest which it has excited would seem almost to have produced forgetfulness of the fact that many phenomena concerning the *Treponema pallida* and the Wassermann reaction still await explanation. Therefore, Jesionek's article may help us to regain some of our lost perspective with regard to the Wassermann method of serodiagnosis.

The articles on the subject are arranged, for the purpose of this critical review, into two groups. In the first are placed those papers which have to do with the chemistry and the technic of the reaction. This group need not be considered here as it has been so recently reviewed in this journal by Lucas.[1] We may, therefore, confine our attention to the second division which deals with the literature on the clinical relationship of the reaction to syphilitic disease.

Jesionek concludes from his study that it may be accepted without further comment that the Wassermann reaction gives a positive guide in the presence of *active* cutaneous manifestations of disease; when positive, always declaring them to be syphilis. When, however, the intermediate cases are encountered, in which the cutaneous manifestations are dubious or lacking, it would seem that even the positive Wassermann reaction is not entirely convincing.

In order to demonstrate the value of the reaction and its interpretation, Jesionek has subdivided the articles of the second group. First, he takes up those on the question of the clinical specific nature of the reaction. His conclusion, given in his own words, is that the original idea of a clinical specificity of the reaction for syphilis cannot be

*Jesionek, A.: Praktische Ergebnisse auf dem Gebiete der Haut- und Geschlechtskrankheiten, i, 286, 1912.

1. Lucas, W. P.: The Wassermann Reaction in Syphilis: A Résumé of Current Literature, AM. JOUR. DIS. CHILD., 1912, iii, 259.

sustained from either a biologic or a clinical point of view. As a matter of fact, there is a large number of diseases, besides syphilis, in which one can, now and then, obtain a positive reaction. First of all in this connection, Jesionek mentions frambesia tropica, lepra, scarlet fever and the trypanosome diseases. Of chief interest to the pediatrist, however, is the statement that *scarlet fever* gives a *positive reaction* in approximately 40 per cent. of the cases. Naturally, the need of a differential diagnosis between syphilis and scarlet fever is a rarity.

In commenting on the occurrence of the positive reaction in these non-syphilitic affections, it is stated that one causative factor may be the difficulty of the technic. This factor would apply equally well to every reported reaction, as the method demands that none but the most highly trained specialists shall attempt it. His comment is, therefore, that, before accepting the apparent results of the test, we should examine into the conditions under which the test is made. Nevertheless, there is no question, even on these grounds, but what the test reacts positively in certain non-syphilitic diseases as is manifested by the reports of a number of especially well qualified investigators. According to Weil and Braun, in all these non-syphilitic cases with positive reactions the one common factor present is a morbid alteration of the organs, cell changes and resorption of cell products. These exceptions do not injure the practical meaning of the reaction, but merely call attention to the need of care in estimating the significance of individual factors. Jesionek quotes Lesser as saying:

> **There is never a positive reaction except in the presence of syphilis or a justified suspicion of syphilis—to which we wish to add the words Cave Scharlach.**
>
> **As a matter of practice one would do well, in the presence of a positive reaction, to think first of syphilis, at the same time remembering that occasionally, although seldom, there occur in connection with other diseases such alterations in the blood serum as find their visible expression in the positive result of the reaction of complement-fixation.**

According to the investigations of Seligman and Blume, it seems as if such affections as tumors, phthisis and sepsis, which cause "a powerful consumption," have a tendency to form substances which may give a positive reaction with one or another extract. Furthermore, it is noticeable that the reaction is very frequently positive in sera obtained after death.

In regard to the relationship of the reaction to syphilis as revealed by the literature, Jesionek asks: "Do all syphilitics give a positive reaction?" "If not, why does the reaction behave differently in one case of syphilis than in another? What conclusions are to be drawn from the variable results of the reaction in the individual syphilitics?" He then gives the general answer that a positive reaction is present in nearly every case in which the symptoms are florid. That is to say, not every case

which we may consider syphilitic on the ground of its history or clinical symptoms gives a positive reaction. In general, it can be said that the statistics at hand establish the fact that a positive reaction is obtained in only about 50 per cent. of the total cases of acknowledged syphilis. From this fact is drawn the fundamental conclusion that the negative reaction has no value in the differential diagnosis of syphilis or non-syphilis. Under no condition does a single negative reaction justify the conclusion that syphilis does not exist.

Next, in order to make clearer the meaning of the positive reaction and its relation to the syphilitic disease process, Jesionek reviews the subject from the standpoint of the different disease periods. Without going into details, it may be said that, in the primary stage, the reaction does not become positive, as a rule, until after eight or ten weeks, whereas, in the early secondary stage, it is positive almost without exception. The reason given for this difference is that in the first, the early, period of the primary stage, the disease has not yet become a true systemic infection. On the other hand, in and just preceding the secondary period the infectious processes are at their height and the spirochetes have invaded the whole organism.

As already noted, the reaction is occasionally negative even when the symptoms are "florid." In the light of the statement that "before accepting a result we must investigate the manner of its making," the following comments are especially worthy of note:

We cannot at present definitely explain why such cases (the florid) should give a negative reaction. One point, however, should be emphasized, i. e., that more than one blood examination is necessary to firmly establish the negativity of a manifest syphilis. It frequently happens that the positive result of the second examination throws doubt on the negative finding of the first. The great technical difficulties and the numerous sources of error which complicate every examination throw suspicion on every unusual behavior.

Nearly all investigators obtain a smaller percentage of positive results in tertiary syphilids than in secondary. For example, Brück reports positive results in about 90 per cent. of the secondary syphilids, but only 70 to 80 per cent. in the tertiary. Blascho emphasizes the fact that a negative reaction was strikingly frequent in bone affections, even in out-spoken, painful gummata and in undoubted syphilitic bony exostoses. He has also repeatedly found the reaction negative in syphilitic disease of the kidneys. Jesionek believes that the reaction is negative in gummata of the brain quite as frequently as it is in disease of the bones, "which is all the more curious as the parasyphilitic affections of the brain give rise to a positive reaction quite regularly."

On the other hand, as regards the negative reaction, the difficulty of diagnosing tertiary syphilis of the viscera must not be overlooked. One forgets, only too easily, that a "syphilitic" individual can now and then be ill in other than a specific manner.

All in all, however, one may conclude that tertiary syphilis in patients with undoubted syphilitic symptoms yields positive results as frequently as in patients with secondary manifestations. From this fact Jesionek concludes that in the presence of doubtful symptoms the diagnosis must be syphilis if the reaction is positive.

In congenital syphilis the same laws apply as in acquired syphilis. Therefore, it is no surprise to find that the blood of congenital syphilitics, at least so long as they show manifest symptoms, practically always gives a positive reaction. The Wassermann reaction confirms the clinical observation that syphilitic parents may bear children who never show a trace of syphilitic disease. Such children, however, always give a negative reaction to repeated tests. On the other hand, it happens not infrequently that the reaction is positive in children in whom no clinical symptoms have developed, the sole manifestation of their disease, therefore, lying in the alteration in the blood, which is demonstrated by the complement fixation reaction.

The mothers of syphilitic children react positively practically without exception, notwithstanding the fact that they may show no specific, organic changes. As concerns the relationship of the Wassermann reaction to the laws of inheritance, it can be said that immunity does not exist in the sense of the Baumes-Colles law, but that the so-called immune mothers of syphilitic children as a rule react positively. This means that the mothers carry within themselves an active syphilitic poison and are, therefore, subject to the same conditions as other syphilitic individuals.

LATENT SYPHILIS

In any consideration of the relationship of the Wassermann reaction to syphilis its behavior in the so-called "latent periods" must not be overlooked. According to Jesionek, the reaction is present in fewer cases when the disease is "latent" than when active, but is present oftener in the early latent period than in the late. It is a fact of common agreement that there has been discovered no law which governs the appearance of the positive reaction in the late periods of latency. It seems to occur as frequently thirty to forty years after infection as after only five or ten years. Jesionek suggests that latent syphilitics possess a high antibody content and contends that the positive reactions denote the existence of active syphilis in the patients.

Jesionek next discusses the meaning of the term "latency." In his opinion, so long as the case manifests even the slightest trace of disease, the term latent is inappropriate. Therefore, pigmentation from a pre-existing macule or papule, enlarged glands, disturbances of sensation and the like, remove the case in which they occur from the "latent" class. There are cases, however, in which the disease is actually latent. At the

end of the first year and in the second and third years of the disease there may remain not the slightest discoverable trace of the syphilitic infection. Neither glandular infections nor suspicious pigment anomalies exist. The patient enjoys the best of objective and subjective well-being. But, Jesionek continues, it is characteristic of the syphilitic virus to apparently slumber for years and tens of years, only to suddenly wake into activity. The reason we do not know. Possibly, conditions exist in the host which prevent the spirochetes from exercising their pathogenic properties. We know, for example, through histologic research, that in congenital syphilis the organism may be overrun with spirochetes and nevertheless manifest no changes which can be regarded as specific.

Regarding the occurrence of a positive reaction in the late period of latency, Jesionek believes that chance cannot account for the fact that the percentage of cases which, escaping diagnosis during life, are discovered at autopsy to be syphilitic agree so closely with the percentage of cases giving a positive Wassermann reaction in life, notwithstanding the complete absence of clinical symptoms.

Unfortunately, the Wassermann reaction cannot distinguish between cure and latency. In both conditions there is the same lack of symptoms. The Wassermann reaction, however, does not tell us in which case the infectious agent has been destroyed and in which it is liable to burst into activity again. As a rule, the reaction changes from negative to positive as soon as clinical symptoms reappear. Occasionally, however, the change occurs without accompanying clinical signs.

WASSERMANN REACTION AS A SYMPTOM

With this, we come to the weightiest point in the whole subject of the relation of the Wassermann reaction to syphilitic disease processes. The Wassermann reaction is by no means a constant manifestation which is lasting and unfailing in the individual syphilitic infection, like a stigma or a brand-mark. Its positivity comes and goes and comes again, and again disappears, etc. In other words, the positivity of the Wassermann reaction behaves, in its appearances and disappearances, like all the manifestations in the life of the syphilitic individual which we call syphilitic symptoms.

The question is, then, Is the Wassermann reaction perhaps nothing more than a syphilitic symptom? The answer will place the practical meaning of the serologic blood test in the right light.

If the reaction is truly nothing but a symptom, it should be influenced by antisyphilitic treatment. That it is so influenced is abundantly attested. In this connection and in regard to the symptoms of syphilis in general, the fact is to be emphasized that the earlier the treatment is begun and the more energetically it is carried out, the surer and easier it is to cause the reaction to change. The later the stage in which treatment is begun, the more refractory is the disease to the influence of treatment.

If then, Jesionek argues, one admits that the positivity of the reaction can be removed by therapeutic measures, that it is a symptom of syphilis,

that is, a sign of a constitutional-syphilitic condition, one should not be surprised by the irregular behavior of the reaction, especially in the primary stage in which it is now positive, now negative.

If we seek the explanation it will be found that the reaction is negative in the majority of cases during the earlier period of the existence of the primary lesion, but that as the end of the second incubation period is approached it all at once becomes positive; that is, eight to ten weeks after the infection. It is an accepted fact that it takes a variable length of time after the infection and the appearance of the primary lesion for the spirochetes to spread throughout the body from the place of infection. When this generalization of the virus is accomplished the reaction, for the first time, becomes positive. Although on the average this positivization takes places eight to ten weeks after infection and after the primary lesion has appeared, an occasional case is encountered in which the positive reaction precedes the appearance of the primary lesion. In such instances the systemic invasion antedates the first local symptom.

It is the individual factors resident in each individual which determine the type of the syphilitic disease and the character of its course. The protean character of the syphilitic picture is the consequence of the varying reactive conditions in the different patients. Moreover, if the reaction is regarded in the light of a symptom, it is easy to understand this variability, for syphilis has no symptom so characteristic as to be indispensable. For example, there have been cases which lacked glandular manifestations; cases in which there was no outbreak on the skin or the mucous membranes, and cases even of recent syphilis with healthy offspring.

From the foregoing, the conclusion is, that "The occurrence of a positive Wassermann reaction is to be regarded as neither more nor less than a symptom of syphilis which is not limited to a single phase of the disease process, but a symptom which may make itself manifest so soon and so long as active virus exists in the organism." The complement fixation reaction has demonstrated the truth of the clinical observation that the changes in the blood of syphilitics, on which the reaction is based, are referable, on the one hand, to the vitality and the activity of the spirochetes, which cause the disease, and, on the other hand, to the reactive processes on the part of the organism.

In summing up, Jesionek says that "the Wassermann reaction has refined the technic of the diagnostic tests and thereby enabled us to demonstrate the syphilitic poison in cases in which our previous methods of research left us in the lurch. We are no longer obliged to await the appearance of the grosser changes in the skin or in the other organs to recognize the fact that the syphilitic poison threatens the health and the life of a patient. In cases of doubtful diagnosis the positive result of

the Wassermann reaction suffices for the decision. If we already suspect the specific nature of an affection on clinical grounds we remember, in regard to the positivity of the Wassermann reaction, that undoubted syphilitic symptoms are also "so good as regularly" accompanied by a positive Wassermann reaction. Naturally, the same rule holds in regard to the symptom of the positivity of the reaction as applied to every other syphilitic symptom: a single symptom, by itself, is never absolute proof. The positivity of the Wassermann reaction is not pathognomonic in the strict sense of the word. For that matter, neither is a macular eruption. When, however, we bring all the suspicious appearances together each single symptom gains in importance. "Of all symptoms which compose the picture of syphilis the Wassermann reaction is perhaps the most reliable."

As regards its relation to prognosis, Jesionek is of the opinion that "lies the infection never so far in the past, the Wassermann reaction is the sign that the patient is syphilitic." He then goes on to state that the reaction yields as little information concerning infectiousness as does the presence of a periostitis or a gumma. A positive reaction by no means indicates that the patient must transmit his syphilis to his children. Neisser is quoted to the effect that a positive reaction does not, of itself, demand that marriage shall be forbidden, as often in such cases the parents beget healthy children and themselves never again manifest a trace of the disease. If at least four years have passed since the infection, if during this period satisfactory treatment has been given and if there has been no symptom during the last year at least, marriage must be permitted. Nevertheless, as long as the Wassermann reaction remains positive no one can guarantee that some form of the syphilitic disease may not manifest itself in the offspring.

TREATMENT

As regards the treatment of syphilis, the physician no longer waits for the appearance of undoubted macroscopic symptoms, but begins treatment immediately on the first appearance of the Wassermann reaction. This is directly in line with the statement previously made that the earlier in the course of the disease treatment is instituted the easier it is to overcome the infection.

Discussing the old question as to the proper time at which to begin systemic antisyphilitic treatment, Jesionek states that the latest, although sparse, experiences seem to indicate that it is senseless to saturate the organism with mercury so long as the reaction is negative.

The failure of so-called preventive treatment when the evidence of the generalization of the virus is lacking seems to indicate that mercury has not in itself the power to kill or to paralyze the parasite. It does, however, possess the ability to aid the organism in its struggle. It is

only after the organism has itself begun to fight that external remedies are able to play an active part. The reactive process which we call the specific-disease-symptoms is evidence that the organism is working in its own defense. Therefore, the time to institute general treatment is that time in the primary stage when the Wassermann reaction first becomes positive.

Unfortunately, although the positive reaction may be changed tc a negative through therapeutic measures, it is not possible to affirm with certainty that a cure has been attained as, in spite of a negative reaction, the poison may still remain in the organism.

RECAPITULATION

The chief points brought out by this summary of the literature on the Wassermann reaction are, in their order, as follows:

The Wassermann reaction gives a positive guide in the presence of *active* cutaneous manifestations, but is not entirely convincing when the cutaneous symptoms are dubious or lacking.

The Wassermann reaction is not specific for syphilis. It is positive more or less frequently in a considerable number of other diseases.

The technic is so exceedingly difficult and the sources of error so numerous as to render acceptance of results reported dependent on the qualifications possessed by the maker of the test.

The statistics at hand seem to show that the test responds positively in only about 50 per cent. of the total cases.

Therefore, the fundamental conclusion is drawn that the negative reaction has no diagnostic value.

Considered from the point of view of the period of disease, the reaction does not become positive in the primary stage until after a considerable lapse of time; usually eight to ten weeks from the time of the infection. Occasionally, it occurs as early as the third week. During the secondary period, when the activity of the disease is at its height, the reaction is positive with scarcely an exception. The positive reaction is considerably less frequent in the tertiary period, considered as a whole, although, in the presence of undoubted syphilitic symptoms, it is quite constant.

The same laws govern the behavior of the Wassermann reaction in congenital syphilis as in acquired syphilis.

Syphilitic parents with a positive Wassermann reaction may bear children with no trace of the disease and with a persistently negative reaction; or may bear children with no clinical signs of disease, but giving a positive reaction.

The mothers of syphilitic children are immune because, according to the Wassermann reaction, they are themselves syphilitic.

Periods of latency occur during the course of syphilis when no clinical signs of disease can be discovered. The reaction is positive less frequently

during these "latent" periods than during the periods of activity, especially if the "latency" occurs late in the course of the syphilitic disease.

The percentage of positive reactions found during the period of "late latency" agrees very closely with the percentage of cases undetected during life, but demonstrated at the autopsy to be syphilitic.

"Latency" may be due to cure (when the symptoms of disease never recur) or to "slumber" (when for some as yet unknown reason manifestations may unexpectedly develop at some future time). The Wassermann reaction does not distinguish between the negative reaction resulting from cure and the negative reaction from an infection which merely "slumbers."

The fact that the reaction, negative in the "latent" period, promptly becomes positive when the infection again becomes active, is very suggestive.

It follows from the statements above that the Wassermann reaction is not a constant and invariable accompaniment of the syphilitic disease process, but comes and goes just as do the other individual manifestations of the infection.

The Wassermann reaction is to be regarded as neither more nor less than a symptom which manifests itself in the presence of active disease processes regardless of the stage of the disease. In other words, it is not the period of the disease on which the occurrence of the complement fixation depends, but on the activity of the invading parasite.

When the Wassermann reaction is positive, but lacks clinical confirmation, the suggestion of the existence of a syphilitic process is exceedingly strong, but not absolutely beyond debate. When, however, the reaction is positive in the presence of manifest, or even merely suspicious, symptoms, the doubt is changed to a practical certainty by the fact of its occurrence.

Notwithstanding the statement just made, the tendency is to regard the occurrence of a positive reaction as positive evidence of the existence of active syphilis even when lacking confirmatory evidence.

A negative Wassermann test is of no value in prognosis. Apparently, the persistence of the positive reaction under certain conditions has no more value than the negative, as was shown in the discussion of the relation of the test to marriage.

Although the aim from a therapeutic point of view is to convert a positive reaction into a negative, so far as the Wassermann reaction is concerned, we cannot say whether the invading spirochetes have actually been conquered or only temporarily paralyzed. In short, our understanding of the inner meaning of the Wassermann reaction is incomplete and practically limited to the positive phase of the question. But our knowledge of even the positive phase lacks perfection.

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